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Draft Plan for Review of the Primary National Ambient Air Quality Standard for Carbon Monoxide

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U. S. Environmental Protection Agency

National Center for Environmental Assessment
Office of Research and Development
and
Office of Air Quality Planning and Standards
Office of Air and Radiation

Research Triangle Park, North Carolina 2771

DISCLAIMER

This integrated review plan serves as a public information document and as a management tool for the U.S. Environmental Protection Agency's National Center for Environmental Assessment and the Office of Air Quality Planning and Standards in conducting the review of the national ambient air quality standards for carbon monoxide. The approach described in this plan may be modified to reflect information developed during this review and to address advice and comments received from the Clean Air Scientific Advisory Committee and the public throughout this review. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

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1.   INTRODUCTION

The U.S. Environmental Protection Agency (EPA) is conducting a review of the air quality criteria for carbon monoxide (CO) and the primary (health-based) national ambient air quality standards (NAAQS) for carbon monoxide (CO). The purpose of this document is to communicate the plan for this review.[1]

This review will provide an integrative assessment of relevant scientific information for CO and will focus on the basic elements of the primary standards: the indicator, averaging times, forms, and levels. These elements, which serve to define each ambient air quality standard, must be considered collectively in evaluating the health protection afforded by the standard. The existing primary CO standards include a 1-hour standard set at 35 parts per million (ppm), and an 8-hour standard set at 9 ppm, neither to be exceeded more than once per year.

This review plan is organized into six chapters. Chapter 1 presents background information on the review process, the legislative requirements for the review of the NAAQS, and past reviews of the NAAQS for CO. Chapter 2 presents the current review schedule. Chapter 3 presents a set of policy-relevant questions that will serve to focus this review on the critical scientific and policy issues. Chapters 4 through 6 discuss the planned scope and organization of the key assessment documents, the planned approaches for preparing the documents, and plans for scientific and public review of the documents.

1.1   OVERVIEW OF THE REVIEW PROCESS

The Agency has recently decided to make a number of changes to the process for reviewing the NAAQS (described at http://www.epa.gov/ttn/naaqs/). In making these changes, the Agency consulted with the Clean Air Scientific Advisory Committee (CASAC),[2] which provides advice to the Administrator on key elements of NAAQS reviews, and the public. This new process, which is being applied to the current review of the NAAQS for CO, contains four

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[1] This plan will generally refer to the review of the primary standard for CO because there is currently no secondary NAAQS for CO to review.   However, the scope of EPA's review will include consideration of whether, based on the revised air quality criteria for CO, it is appropriate to propose a new secondary standard.
[2] See http://yosemite.epa.gov/sab/sabproduct.nsf/WebCASAC/CommitteesandMembership?OpenDocument for a list of CASAC members.

1   major components: an integrated review plan, a science assessment, a risk/exposure assessment,

2   and a policy assessment/rulemaking. Each of these components is described in this section.

3   The review process starts with the development of an integrated review plan prepared

4   jointly by EPA's National Center for Environmental Assessment (NCEA) within the Office of

5   Research and Development (ORD) and EPA's Office of Air Quality Planning and Standards

6   (OAQPS) within the Office of Air and Radiation (OAR). This document represents the current

7   plan and specifies the schedule for the entire review, the process for conducting the review, and

8   the key policy-relevant science issues that will guide the review.

9   The second component of the review process is the development of the science

10 assessment, which consists of an Integrated Science Assessment (ISA) and supporting annexes.

11 NCEA along with contracted support prepares these documents. The annexes will contain a

12 comprehensive description and evaluation/assessment of the full breadth of the current scientific

13 literature pertaining to known and anticipated effects on public health and welfare associated

14 with CO in the ambient air, emphasizing the information that has become available since the last

15 review in order to reflect the current state of knowledge. NCEA will then critically evaluate,

16 integrate, and synthesize the most policy-relevant science from the annexes into an ISA. The ISA

17 is intended to provide information useful in forming judgments about air quality indicator(s),

18 form(s), averaging time(s) and level(s) for the CO NAAQS. Hence, the ISA and its associated

19 annexes function in the new NAAQS review as the Air Quality Criteria Document (AQCD) did

20 in previous reviews. The schedule includes production of a first and second draft ISA, both of

21 which will undergo CASAC and public review prior to completion of the final ISA. Section 4

22 provides a more detailed description of the planned scope, organization and assessment approach

23 for the annexes and ISA.

24   In the third component of the revised review process, the risk/exposure assessment, EPA's

25 Office of Air Quality Planning and Standards (OAQPS) plans to draw upon the information

26 presented in the ISA to develop quantitative and qualitative estimates of the exposures and risks

27 of adverse health effects associated with current ambient levels of CO, with levels that just meet

28 the current standards, and with levels that just meet possible alternative standards. Section 5 of

29 this integrated plan contains more detail about possible approaches EPA could take in

30 conducting the human health assessments. Once the first draft ISA is complete, EPA will release

31 a draft Scope and Methods Plan for human health assessments that CASAC and the public will

1 review. The Scope and Methods Plan will describe the proposed scope of the analyses to be

2 performed and the tools/methods that may be employed. Comments on the draft Scope and

3 Methods Plan will be considered as EPA performs the actual analyses. The schedule includes

4 production of first and second draft risk/exposure assessments, all of which will undergo

5 CASAC and public review prior to completion of the final risk/exposure assessment reports that

6 will focus on key results, observations, and uncertainties.

7   The fourth component of the revised process will be a policy assessment/rulemaking.

8 Under the new process, a staff paper, such as that prepared in previous NAAQS reviews, will not

9 be prepared. Rather, Agency views on policy options will be published in the Federal Register

10 as an advance notice of proposed rulemaking (ANPR). The ANPR will present a policy

11 assessment and will be accompanied by supporting documents, such as air quality analyses and

12 technical support documents, as appropriate.   Taking into account CASAC advice and

13 recommendations as well as public comment on the ANPR, the Agency will publish a proposed

14 action, to be followed by a public comment period. Considering comments received on the

15 proposed action, the Agency will issue a final decision to complete the review.

16

17 **1.2   LEGISLATIVE REQUIREMENTS**

18   Two sections of the Clean Air Act (CAA) govern the establishment and revision of the

19 NAAQS. Section 108 (42 U.S.C. 7408) directs the Administrator to identify and list air

20 pollutants that "in his judgment, cause or contribute to air pollution which may reasonably be

21 anticipated to endanger public health and welfare" and whose "presence . . . in the ambient air

22 results from numerous or diverse mobile or stationary sources" and to issue air quality criteria

23 for those that are listed. Air quality criteria are intended to "accurately reflect the latest scientific

24 knowledge useful in indicating the kind and extent of identifiable effects on public health or

25 welfare which may be expected from the presence of [a] pollutant in ambient air . . . ."

26   Section 109 (42 U.S.C. 7409) directs the Administrator to propose and promulgate

27 "primary" and "secondary" NAAQS for pollutants listed under section 108. Section 109(b)(1)

28 defines a primary standard as one "the attainment and maintenance of which in the judgment of

29 the Administrator, based on such criteria and allowing an adequate margin of safety, are requisite

1   to protect the public health."[3] A secondary standard, as defined in section 109(b)(2), must

2   "specify a level of air quality the attainment and maintenance of which, in the judgment of the

3   Administrator, based on such criteria, is requisite to protect the public welfare from any known

4   or anticipated adverse effects associated with the presence of [the] pollutant in the ambient air."[4]

5   The requirement that primary standards include an adequate margin of safety was

6   intended to address uncertainties associated with inconclusive scientific and technical

7   information available at the time of standard setting. It was also intended to provide a reasonable

8   degree of protection against hazards that research has not yet identified. See *Lead Industries*

9   *Association v. EPA*, 647 F.2d 1130, 1154 (D.C. Cir 1980), cert. denied, 449 U.S. 1042 (1980);

10   *American Petroleum Institute v. Costle*, 665 F.2d 1176, 1186 (D.C. Cir. 1981), cert. denied, 455

11   U.S. 1034 (1982). Both kinds of uncertainties are components of the risk associated with

12   pollution at levels below those at which human health effects can be said to occur with

13   reasonable scientific certainty. Thus, in selecting primary standards that include an adequate

14   margin of safety, the Administrator is seeking not only to prevent pollution levels that have been

15   demonstrated to be harmful but also to prevent lower pollutant levels that may pose an

16   unacceptable risk of harm, even if the risk is not precisely identified as to nature or degree.

17   In selecting a margin of safety, the EPA considers such factors as the nature and severity

18   of the health effects involved, the size of sensitive population(s) at risk, and the kind and degree

19   of the uncertainties that must be addressed. The selection of any particular approach to

20   providing an adequate margin of safety is a policy choice left specifically to the Administrator's

21   judgment. See *Lead Industries Association v. EPA*, supra, 647 F.2d at 1161-62.

22   In setting standards that are "requisite" to protect public health and welfare, as provided in

23   section 109(b), EPA's task is to establish standards that are neither more nor less stringent than

24   necessary for these purposes. In so doing, EPA may not consider the costs of implementing the

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[3] The legislative history of section 109 indicates that a primary standard is to be set at "the maximum permissible ambient air level . . . which will protect the health of any [sensitive] group of the population," and that for this purpose "reference should be made to a representative sample of persons comprising the sensitive group rather than to a single person in such a group" S. Rep. No. 91-1196, 91st Cong., 2d Sess. 10 (1970).

[4] Welfare effects as defined in section 302(h) (42 U.S.C. 7602(h)) include, but are not limited to, "effects on soils, water, crops, vegetation, man-made materials, animals, wildlife, weather, visibility and climate, damage to and deterioration of property, and hazards to transportation, as well as effects on economic values and on personal comfort and well-being."

1   standards. See generally *Whitman v. American Trucking Associations*, 531 U.S. 457, 465-472,

2   475-76 (2001).

3   Section 109(d)(1) requires that "not later than December 31, 1980, and at 5-year

4   intervals thereafter, the Administrator shall complete a thorough review of the criteria

5   published under section 108 and the national ambient air quality standards . . . and shall make

6   such revisions in such criteria and standards and promulgate such new standards as may be

7   appropriate . . . ." Section 109(d)(2) requires that an independent scientific review committee

8   "shall complete a review of the criteria . . . and the national primary and secondary ambient air

9   quality standards . . . and shall recommend to the Administrator any new . . . standards and

10   revisions of existing criteria and standards as may be appropriate . . . ." Since the early 1980's,

11   this independent review function has been performed by the Clean Air Scientific Advisory

12   Committee (CASAC) of EPA's Science Advisory Board.

13

14   **1.3   HISTORY OF REVIEWS OF THE PRIMARY NAAQS FOR CO**

15   On April 30, 1971, EPA promulgated identical primary and secondary NAAQS for CO,

16   under section 109 of the Act, set at 9 parts per million (ppm), 8-hour average and 35 ppm, 1-hour

17   average, neither to be exceeded more than once per year (36 FR 8186). In 1979, EPA published

18   *Air Quality Criteria Document for Carbon Monoxide* (AQCD) (US EPA, 1979a), which updated

19   the scientific criteria upon which the initial CO standards were based. A Staff Paper (US EPA,

20   1979b) was prepared and, along with the AQCD, served as the basis for development of

21   proposed rulemaking (45 FR 55066) published on August 18, 1980. Delays due to uncertainties

22   regarding the scientific basis for the final decision resulted in EPA's announcing a second public

23   comment period (47 FR 26407). Following substantial reexamination of the scientific data, EPA

24   prepared an Addendum to the 1979 AQCD (EPA, 1984a) and an updated Staff Paper (US EPA,

25   1984b). Following review by CASAC, EPA announced its final decision (50 FR 37484) not to

26   revise the existing primary standard and to revoke the secondary standard for CO on September

27   13, 1985.

28   In 1987, EPA initiated action to revise the criteria for CO and released a revised AQCD

29   for CASAC and public review. In a "closure letter" (McClellan, 1991) sent to the Administrator,

30   the CASAC concluded that the AQCD (US EPA, 1991) ". . . provides a scientifically balanced

31   and defensible summary of current knowledge of the effects of this pollutant and provides an

1   adequate basis for the EPA to make a decision as to the appropriate primary NAAQS for CO."

2   A revised Staff Paper subsequently was reviewed by CASAC and the public, and in a "closure

3   letter" (McClellan, 1992) sent to the Administrator, it was stated ". . . that a standard of the

4   present form and with a numerical value similar to that of the present standard would be

5   supported by the present scientific data on health effects of exposure to carbon monoxide."

6   Based on the revised AQCD (US EPA, 1991) and staff conclusions and recommendations

7   contained in the revised Staff Paper (US EPA1992), the Administrator announced the final

8   decision (59 FR 38906) on August 1, 1994, that revision of the primary NAAQS for CO was not

9   appropriate.

10   In 1997, revisions to the AQCD were initiated. A workshop was held in September 1998

11   to review and discuss material contained in the revised AQCD. On June 9, 1999, the CASAC

12   held a public meeting to review the draft AQCD and a draft exposure analysis methodology

13   document. Comments from CASAC and the public were considered in a second draft AQCD,

14   which was reviewed at a CASAC meeting held on November 18, 1999. After revision of the

15   second draft AQCD, the final AQCD (US EPA, 2000) was released in August 2000. EPA put

16   the review on hold when Congress called on the National Research Council (NRC) to conduct a

17   review of the impact of meteorology and topography on ambient CO concentrations in high

18   altitude and extreme cold regions of the U.S. In response, the NRC convened the committee on

19   Carbon Monoxide Episodes in Meteorological and Topographical Problem Areas, which focused

20   on Fairbanks, Alaska as a case study in an interim report, which was completed in 2002. A final

21   report, "Managing Carbon Monoxide Pollution in Meteorological and Topographical Problem

22   Areas," was published in 2003 (NRC, 2003) and offered a wide range of recommendations on

23   management of CO air pollution, cold start emissions standards, oxygenated fuels, and CO

24   monitoring. EPA did not complete the review which started in 1997.

25

26   **1.4   SCOPE OF THE REVIEW**

27   For the current review of the primary CO standard, relevant scientific information on

28   human exposures and health effects associated with exposure to ambient CO will be assessed.

29   The possible influence of other atmospheric pollutants on the interpretation of the role of CO in

30   health effects studies will be considered. This will include other pollutants with the potential to

31   co-occur in the environment (e.g., NO_2, SO_2, O_3, and PM). The review will also assess any

1   relevant scientific information associated with known or anticipated public welfare effects that

2   may be identified.

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2. REVIEW SCHEDULE

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2   In September 2007, EPA's National Center for Environmental Assessment in Research

3   Triangle Park, NC (NCEA-RTP) announced the initiation of the current periodic review of the

4   air quality criteria for CO and the CO NAAQS and issued a call for information in the Federal

5   Register (72 FR 52369). Table 2-1 outlines the schedule under which the Agency is currently

6   conducting this review.[5]

Table 2-1. Proposed Schedule for Development of Revised CO Integrated Science Assessment (ISA) and CO Primary Standard

Stage of Review	Major Milestone	Draft Target Dates
Integrated Plan	Literature Search	Ongoing
	Federal Register Call for Information	September 2007
	Workshop on science/policy issues	January 2008
	Draft CO NAAQS Integrated Review Plan	March 2008
	CASAC consultation	April 2008
	Prepare final integrated CO NAAQS Work Plan	April 2008
Science Assessment	Prepare first draft of ISA	June 2009
	CASAC/public review first draft ISA	August 2009
	Prepare second draft of ISA	January 2010
	CASAC/public review second draft ISA	March 2010
	Prepare final ISA	May 2010
Risk/Exposure Assessment	Prepare assessment methodology	June 2009
	CASAC/public consultation on methodology	August 2009
	Prepare first draft risk and/or exposure assessments	January 2010
	CASAC/public review of the first draft	March 2010
	Prepare second draft of risk and/or exposure assessments	September 2010
	CASAC/public review of second draft assessments	November 2010
	Prepare final assessments	January 2011
	Prepare first draft risk and/or exposure assessments	January 2010
Policy Assessment/ Rulemaking	Advanced Notice of Public Rulemaking (ANPR)	February 2011
	CASAC review/public comment on ANPR	April 2011
	Proposed rulemaking	October 2011
	Final rulemaking	July 2012

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[5] This schedule is subject to change pending issuance of a court-ordered schedule that will govern the completion of the review.

3. KEY POLICY-RELEVANT ISSUES

3.1 HISTORICAL PERSPECTIVE

The most recent review of the NAAQS for CO, completed in 1994, concluded that exposure to CO is associated with a variety of acute health effects, but there was very limited evidence of chronic effects. This review resulted in EPA's conclusion that the existing primary CO NAAQS provide adequate protection from health effects associated with 1-hour and 8-hour exposures to ambient CO. A separate long-term standard was not recommended. The current levels for the 1-hour and 8-hour primary NAAQS for CO are 35 ppm and 9 ppm, respectively.

3.2 ISSUES TO BE CONSIDERED IN THE CURRENT REVIEW

In this review, a series of policy-relevant questions will frame our approach to determining whether the current primary NAAQS for CO should be retained or revised. The answers to these questions, and the resulting conclusions regarding the corresponding policy issues, will inform the decision of whether to retain or revise the current short-term (1- and 8-hour) standards.

The first step in reviewing the adequacy of the current primary standard is to consider whether the available body of scientific evidence, assessed in the ISA, supports or calls into question the scientific conclusions reached in the last review regarding health effects related to exposure to CO in the ambient air. This evaluation of the newly available scientific evidence will address a series of questions including the following:

- Has new information altered the scientific support for the occurrence of health effects following short- and/or long-term exposure to levels of CO found in the ambient air?
- To what extent is key evidence becoming available that could inform our understanding of subpopulations that are particularly sensitive to CO exposures? Specifically, is there new or emerging evidence on health effects beyond cardiovascular and respiratory endpoints (e.g., systemic effects, developmental effects, birth outcomes) that suggest additional sensitive subpopulations should be given increased focus in this review (e.g., fetuses, neonates)?

- What do recent studies focused on the near-roadway environment tell us about high-exposure subpopulations and the health effects of CO?
- At what levels of CO exposure do health effects of concern occur?
- To what extent is key scientific evidence becoming available to improve our understanding of the health effects associated with various time periods of CO exposures, including not only daily, but also chronic (months to years) exposures? To what extent is critical research becoming available that could improve our understanding of the relationship between various health endpoints and different lag periods (e.g., single day, multi-day distributed lags)?
- To what extent does the evidence suggest that alternate dose indicators other than carboxyhemoglobin (COHb) levels should be evaluated (e.g., percent oxygen saturation)?
- Has new information altered conclusions from previous reviews regarding the plausibility of adverse health effects caused by CO exposure?
- To what extent have important uncertainties identified in the last review been reduced and/or have new uncertainties emerged?

If the evidence suggests that revision of the current standard might be appropriate, we will consider whether the available body of evidence supports consideration of options that are different from the current standard. The following questions will inform this determination:

- Is there evidence for the occurrence of adverse health effects at levels of CO lower than those observed previously? If so, at what levels and what are the important uncertainties associated with that evidence?
- Do exposure estimates suggest that exposures of concern for CO-induced health effects will occur? If so, are these exposures of sufficient magnitude such that the health effects might reasonably be judged to be important from a public health perspective? What are the important uncertainties associated with these exposure estimates?
- Do health effects evidence and air quality/exposure assessments provide support for considering different exposure indices or averaging times?

1   ▪ What range of levels is supported by the health effects evidence and air
2   quality/exposure assessments, and what are the uncertainties and limitations in the
3   health effects evidence and air quality/exposure assessments?
4   ▪ What is the range of forms supported by the health effects evidence and air
5   quality/exposure assessments, and what are the uncertainties and limitations in that
6   health effects evidence and air quality/exposure assessments?
7

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4.   SCIENCE ASSESSMENT

4.1   SCOPE AND ORGANIZATION

The science assessment for CO will consist of the ISA and its supporting annexes. The ISA will critically evaluate and integrate the scientific information on exposure and health effects associated with CO in ambient air. The annexes, which will evaluate and summarize relevant studies, will provide more detailed information from the most pertinent scientific literature in support of the ISA. The annexes will include scientific evidence organized by health outcome in the discipline areas of epidemiology, toxicology, controlled human exposures (human clinical studies), and dosimetry, as well as human exposure and atmospheric science relevant to the review of the primary CO NAAQS. The ISA will draw from this evidence and synthesize the current state of knowledge on the most relevant issues pertinent to the review of the NAAQS for CO. A formal framework for the integration of health effects evidence, based on approaches formulated by other regulatory and science agencies, has been developed for the second external review draft ISA for NO_x (U.S. EPA, 2008) and will be applied in the current CO review. Information from the scientific disciplines listed above will be integrated into the health effects evidence in order to contribute to a better understanding of population exposure and/or risk, or to a better understanding of the nature, sources, distribution, measurement, and/or concentrations of CO in ambient air. The ISA discussions will be designed to focus on the key policy questions described in Section 3 of this document.

The focus of the ISA will be on literature identified since the previous review of the air quality criteria for CO and on key science and policy issues raised during the last review. Findings and conclusions from the 2000 Air Quality Criteria Document (US EPA, 2000) for CO will be briefly summarized at the beginning of the ISA. The results of new studies will be integrated with previous findings. Important older studies will be more specifically discussed if they remain definitive or are open to reinterpretation in light of newer data. Information that has undergone scientific peer review and that has been published (or accepted for publication) in the open literature will be considered. Additionally, official studies and reports from governmental agencies, may be included, as appropriate. Emphasis will be placed on studies conducted at or near CO concentrations found in ambient air. In recognition of the fact that toxicologic and

1 human clinical studies do not necessarily reflect effects in the most sensitive population, studies

2 at higher exposure levels will be included when they provide information relevant to previously

3 unreported effects, evidence of the potential mechanism for an observed effect, or information on

4 exposure-response relationships.

5

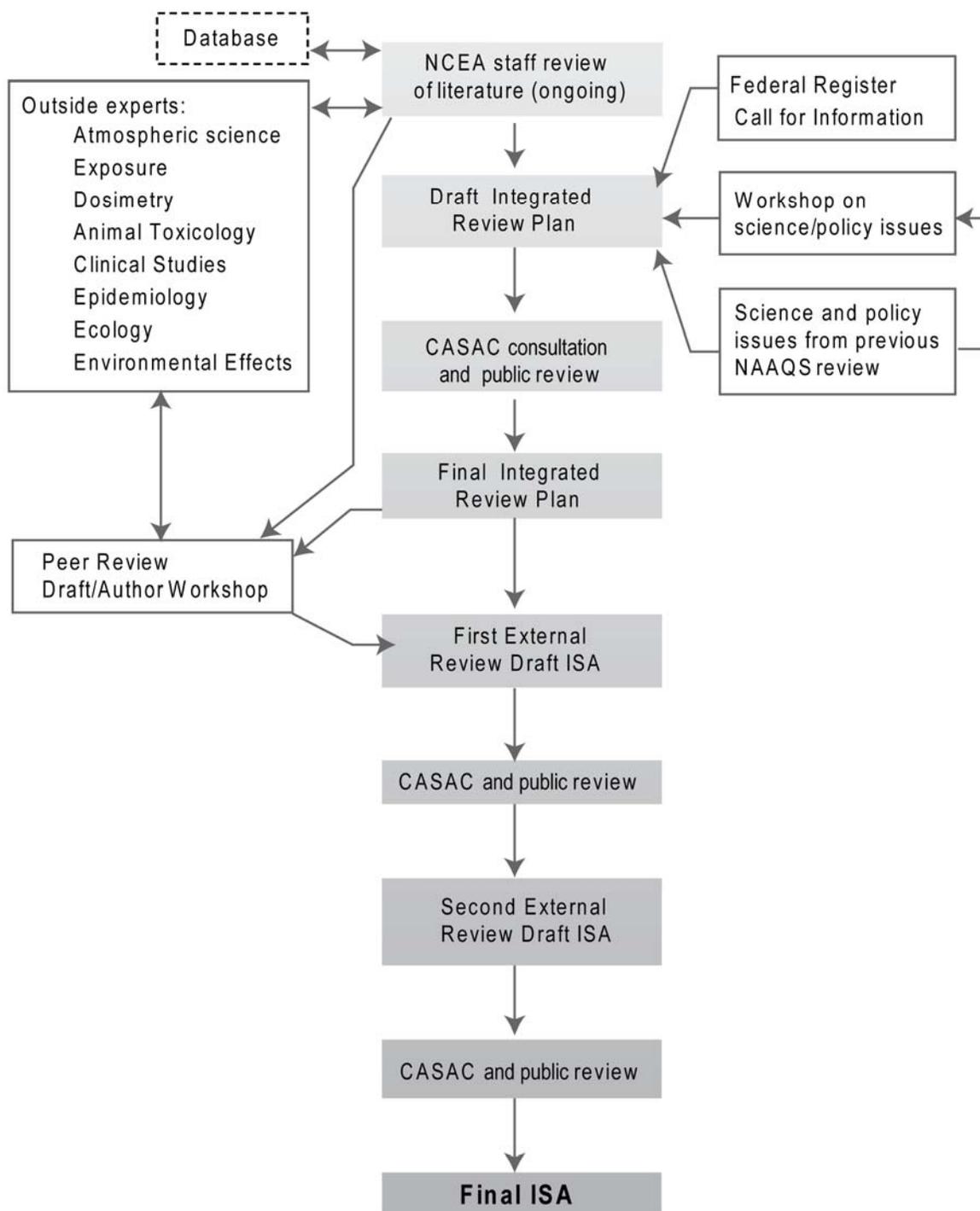6 **4.2   ASSESSMENT APPROACH**

7

8 **Introduction**

9   The EPA's National Center for Environmental Assessment in Research Triangle Park

10 (NCEA-RTP) is responsible for preparing the ISA and the related annexes for CO. Expert

11 authors include EPA staff with extensive knowledge in their respective fields and extramural

12 scientists contracted to the EPA. A diagram showing the standard protocol for development of

13 an ISA, including both health and ecosystem effects, is presented in Figure 4.1. While no

14 secondary standard currently exists for CO, any evidence of welfare effects (e.g., ecosystem

15 effects) of ambient CO identified during ISA development will also be included. The ISA for

16 CO will focus primarily on scientific evidence relating to health effects. A complete description

17 of the new NAAQS review process is presented in Section 1.1.

18

Standard Protocol for ISA Development

Database → NCEA staff review of literature (ongoing)

Outside experts:
   Atmospheric science
   Exposure
   Dosimetry
   Animal Toxicology
   Clinical Studies
   Epidemiology
   Ecology
   Environmental Effects

Federal Register Call for Information

Draft Integrated Review Plan

Workshop on science/policy issues

CASAC consultation and public review

Science and policy issues from previous NAAQS review

Final Integrated Review Plan

Peer Review Draft/Author Workshop

First External Review Draft ISA

CASAC and public review

Second External Review Draft ISA

CASAC and public review

Final ISA

1

2

3 **Figure 4.1. Protocol for ISA development, showing the steps involved in production of**

4 **Integrated Science Assessments.**

5

Literature Search

    The NCEA-RTP will use a systematic approach to identify relevant studies for consideration. A Federal Register Notice (72 FR 52369, September 13, 2007) was published to announce the initiation of this review and request information from the public. An initial publication database will be established by searching the online databases MEDLINE, Toxfile, Pascal, Biosis, and Embase using as key words terms including carbon monoxide, methane, carbon dioxide, CO, CH_4, CO_2, hydroxyl radical, carboxyhemoglobin, COHb, hypoxia, traffic, and combustion. Targeted searches will also be conducted to identify articles relevant to specific health and physical science disciplines. As appropriate, the search strategies will be periodically reexamined and modified to enhance identification of pertinent published papers. Additional papers will be identified for inclusion in the publication base in several ways. These include the review of pre-publication tables of contents for journals in which relevant papers may be published, as well as independent identification of relevant literature by expert authors. In addition, publications that may be pertinent are identified by both the public and CASAC during the external review process. The studies identified will include research published or accepted for publication by a date determined to be as inclusive as possible given the relevant target dates in the NAAQS review schedule. Some additional studies, published after that date, may also be included if they provide new information that impacts one or more key scientific issues. The combination of these approaches should produce the comprehensive collection of pertinent studies needed to form the basis of the ISA. The following sections briefly summarize criteria for selection of studies for this draft ISA.

General Criteria for Study Selection

    In assessing the scientific quality and relevance of epidemiological and human or animal toxicological studies, the following considerations will be taken into account.

- To what extent are the aerometric data, exposure, or dose metrics of adequate quality and sufficiently representative to serve as indicators of exposure to ambient CO?
- Were the study populations adequately selected and are they sufficiently well defined to allow for meaningful comparisons between study groups?
- Are the health endpoint measurements meaningful and reliable?

1   ▪ Does the study contain unique data, such as the documentation of a previously

2   unreported effect, documentation of the mechanism for an observed effect, or

3   information on exposure-response relationships?

4   ▪ Are the statistical analyses appropriate, properly performed, and properly interpreted?

5   ▪ Are likely covariates (i.e., potential confounders or effect modifiers) adequately

6   controlled or taken into account in the study design and statistical analysis?

7   ▪ Are the reported findings internally consistent, biologically plausible, and coherent in

8   terms of consistency with other known facts?

9 Consideration of these issues informs our judgments on the relative quality of individual studies

10 and allows us to focus the assessment on the most pertinent studies.

11

12 **Criteria for Selecting Epidemiological Studies**

13   In selecting epidemiological studies for the present assessment, EPA will consider

14 whether a given study contains information on (1) associations with measured CO concentrations

15 using short- or long-term exposures at or near ambient levels of CO; (2) health effects of CO or

16 indicators related to CO sources (e.g., motor vehicle emissions, fossil fuel combustion);

17 (3) health endpoints and populations not previously extensively researched; (4) multiple

18 pollutant analyses and other approaches to address issues related to potential confounding and

19 modification of effects; and/or (5) important methodological issues (e.g., lag of effects, model

20 specifications, thresholds, mortality displacement) related to CO exposure effects. All selected

21 studies will be considered in the evaluation of the health evidence, including studies conducted

22 in countries outside the United States and Canada. In drawing conclusions or recommendations

23 pertinent for quantitative risk or exposure analyses, particular emphasis will be placed on those

24 relevant to standard setting in the United States. Specifically, studies conducted in the U.S. or

25 Canada will generally be discussed in more detail than those from other geographic regions, as

26 the potential impacts of differing health care systems and the underlying health status of the

27 populations need to be accounted for in the assessment. Emphasis in the text will be placed on

28 discussion of (1) new, multi-city studies that employ standardized methodological analyses for

29 evaluating CO effects and that provide overall estimates for effects based on combined analyses

30 of information pooled across multiple cities; (2) new studies that provide quantitative effect

1   estimates for populations of interest; and (3) studies that consider CO as a component of a

2   complex mixture of air pollutants.

3

4   **Criteria for Selecting Animal and Human Toxicological Studies**

5   Criteria for the selection of research evaluating animal toxicological or controlled

6   exposure studies will focus primarily on those studies conducted within about an order of

7   magnitude of ambient CO concentrations and those studies that approximate expected human

8   exposure conditions in terms of concentration and duration. Studies that elucidate mechanisms

9   of action and/or susceptibility will be considered, with particular emphasis on studies conducted

10   under atmospherically relevant conditions.

11   The selection of research evaluating controlled human exposures to CO will focus on

12   studies in which subjects were exposed at conditions relevant either to ambient exposures or to

13   determination of mechanism. For these controlled human exposures, emphasis will be placed on

14   studies that (1) investigate potentially susceptible populations such as individuals with

15   cardiovascular disease, particularly studies that compare responses in susceptible individuals

16   with those in age-matched healthy controls; (2) address issues such as dose-response or time-

17   course of responses; (3) investigate exposure to CO separately and in combination with other

18   pollutants such as PM, O_3, NO_2 and SO_2; (4) include control exposures to filtered air with

19   subjects serving as their own controls; and (5) have sufficient statistical power to assess findings.

20

21   **Quality Assurance**

22   Important quality assurance measures will be incorporated from the start of the current

23   CO review. EPA uses an NCEA-RTP quality assurance plan for searching scientific literature

24   which details an approach to gathering the scientific information found in peer-reviewed journal

25   articles, books, and government reports. Additionally, NCEA has data quality objectives which

26   identify inputs to the science assessment and provide quality assurance (QA) instruction for

27   researchers citing secondary information.

28

29   **Content and Organization of the ISA**

30   The organization of the ISA for CO will be consistent with that used in the recent draft

31   ISAs for Oxides of Nitrogen and Oxides of Sulfur (US EPA, 2008, 2007). The ISA will contain

1 information relevant to considering whether it is appropriate to retain or revise the current 1-hour

2 and 8-hour standards and whether it is appropriate to consider setting a separate long-term

3 exposure standard. The content of the ISA will be guided by a series of policy-relevant

4 questions derived from the previous review of the CO NAAQS and from the Workshop to

5 Discuss Policy-Relevant Science to Inform EPA's Integrated Plan for the Review of the Primary

6 CO NAAQS, held on January 28-29, 2008 at the EPA campus in Research Triangle Park, NC.

7 These policy-relevant questions are related to two overarching issues. The first issue is whether

8 new evidence reinforces or calls into question the evidence presented and evaluated in the last

9 NAAQS review. The second issue is whether uncertainties from the last review have been

10 addressed and/or whether new uncertainties have emerged. The specific questions that stem

11 from these issues are listed below by topic area.

12

13 **Source to Dose**

14 Air Quality and Atmospheric Chemistry: The ISA will present and evaluate data related to

15 ambient concentrations of CO; sources leading to the presence of CO in the atmosphere; and

16 chemical reactions that determine the formation, degradation, and lifetime of CO in the

17 atmosphere.

18   ▪ What are the strengths and weaknesses of various methods for measuring CO?
19   To what extent are these methods subject to positive or negative sampling artifacts or
20   to interference from other substances?

21   ▪ Based on recent air quality and emissions data, what are current concentrations and
22   emissions of CO? What spatial and temporal patterns can be seen in the air quality
23   data for CO, and how do these relate to patterns of human exposure? What is the
24   effect of averaging time on the level of spatial variability? What are the correlations
25   among ambient concentrations of CO and related pollutants (e.g., NO_x, O_3, PM, SO_x),
26   and how do these change spatially and temporally?

27   ▪ Using air quality and emissions data on CO and atmospheric chemistry models, what
28   are likely policy relevant background concentrations of CO?

29   ▪ Are there other techniques that can be used to better define the range of concentrations
30   and the spatial and temporal variability of CO over the U.S.? Are satellite retrievals or

1   three dimensional chemical transport models useful? Can satellite data be used on a

2   regular basis to improve the characterization of CO emissions?

3   ▪ What information is available on short-term ambient CO concentrations (< 1 hr)?

4

5   Human Exposure: The ISA will evaluate the factors that influence exposure to CO and the

6   uncertainties associated with extrapolation from ambient concentrations to personal exposures to

7   CO of ambient origin, particularly in the context of interpreting results from epidemiologic

8   studies.   The issues of uncertainty differ by the exposure period of interest. Short-term exposure

9   studies (e.g., population-level studies using time-series analyses, field/panel studies) primarily

10   rely on temporal variation in exposure, while long-term exposure studies (e.g., longitudinal

11   cohort studies) rely on spatial variability of exposure.

12   ▪ What data exist on relationships between exposure to CO and corresponding exposure

13   to gaseous and particulate co-pollutants (e.g., NO_x, O_3, PM, SO_x)? What factors affect

14   these relationships (season, housing characteristics, activity patterns, etc.)?

15   ▪ What are the uncertainties when extrapolating between stationary CO monitoring

16   instruments and personal exposure to CO of ambient origin, especially for susceptible

17   groups? Issues include measurement error in outdoor ambient monitors, the use of

18   monitors for estimating community concentrations, and their use as a surrogate for

19   personal exposure to CO of ambient origin.

20   ▪ What do measurements of ambient concentration of CO represent? To what extent do

21   they provide an estimate of ambient exposures for health studies, an indicator of

22   personal exposure to CO, and/or an indicator of personal exposure to other gaseous

23   pollutants (including O_3 and NO_2) and particle phase pollutants generated by traffic?

24   ▪ What influence do the patterns of CO exposure, for both indoor and outdoor sources,

25   have on evaluation of health effects? What is the exposure pattern for indoor sources,

26   such as gas stoves and space heaters (i.e., peak, repeated peak, and average CO) and

27   how does it relate to ambient CO patterns?

28   ▪ What evidence is available on subpopulations likely to have high ambient CO

29   exposures (e.g., those living, working and/or attending school near roadways)?

1   ▪ What data are available to interpret both short- and long-term CO exposures (e.g., <1

2   hour, 1 hour, 8 hours, 24 hours, 2 weeks, or longer)? What data and models are

3   available to support exposure estimates over periods that may be relevant to additional

4   health endpoints, such as birth outcomes? This includes such information as air

5   exchange rates, indoor sources, distance to highways, and performance indicators for

6   methods of measuring personal exposures to CO (particularly at low ambient levels).

7   ▪ How do modeled predictions of CO concentrations compare with monitoring results?

8

9   <u>Dosimetry of Inhaled CO</u>: The ISA will evaluate the literature relating to pharmacokinetic

10   modeling of CO uptake and the associated formation of COHb. Recent information relating to

11   either the well-established Coburn-Forster-Kane model or alternative models will be integrated

12   with literature summarized in the previous AQCD to assess the current state of knowledge on

13   COHb formation. The ISA will assess evidence on uncertainties in modeling COHb as a

14   function of inhaled CO. The contribution of endogenously produced CO to COHb will be

15   considered in the integrative health effects section of the ISA.

16   ▪ What new information is available on the validity and applicability of the Coburn-

17   Forster-Kane model? Are alternative approaches available and preferable for

18   modeling COHb formation from ambient CO?

19   ▪ What factors contribute to uncertainty and variability in estimating COHb formation

20   from ambient CO?

21   ▪ What information is available on COHb formation in fetuses and infants? Issues to be

22   considered include COHb pharmacokinetics in neonates and the relationship between

23   maternal CO exposure and fetal COHb concentration.

24

25   **Health Effects**

26   The ISA will evaluate the literature related to cardiovascular effects (e.g., myocardial

27   ischemia, angina, arrhythmia), central nervous system effects (e.g., loss of dexterity, visual

28   impairment), respiratory effects, and birth outcomes (e.g., low birth weight, preterm birth)

29   associated with short and/or long term exposure to CO. This will include evaluation of

1   emergency department visits, hospitalizations, and mortality associated with these effects.

2   Effects related to other health outcomes identified during the review will also be evaluated.

3   Health effects that are associated with both short- and long-term exposures will be evaluated in

4   epidemiologic, human clinical, and toxicologic studies. Recent studies regarding the formation

5   of endogenous CO by cells and tissues and the resulting biological response will be evaluated in

6   order to determine the relevance to biological responses following ambient CO exposure.

7   Causality, uncertainty, biological mechanism of action, susceptible and vulnerable populations,

8   and public health impact will all be considered. The data will be reviewed with the understanding

9   that effects from ambient CO must be considered in conjunction with co-occurring pollutants

10   (e.g., NO_x, O_3, PM, SO_x).

11   For a given type of health outcome, the ISA will evaluate the strength, robustness and

12   consistency of the findings from the different disciplines. The health findings will be further

13   integrated, using the toxicologic and human clinical studies to assess biologic plausibility and

14   mechanistic evidence for the epidemiology findings. A key focus of the integration of health

15   evidence will be on the attribution of health effects to CO as a component of multipollutant

16   exposures. Efforts will be directed at identifying the lower levels at which effects are observed

17   and at determining concentration-response relationships for CO. Concentration-response

18   relationships among these studies will be evaluated for coherence. The ISA will evaluate the

19   scientific evidence on the occurrence of health effects from long-term or short-term exposure to

20   CO at ambient levels. The ISA will also assess the evidence for uncertainties related to these

21   associations and information on the public health implications related to ambient CO exposure.

22   The evaluation will also focus on which exposure durations and developmental time periods of

23   exposure are most strongly associated with effects, for both short-term and long-term exposures.

24

25   Short-Term Exposure:

26   ▪ What do controlled human exposure, animal toxicologic, and epidemiologic studies

27   indicate regarding the relationship between short-term exposures to CO and health

28   effects of concern (e.g., reduced time to onset of angina pain) in healthy individuals

29   and in those with preexisting disease states (e.g., individuals with cardiovascular

30   disease)? What new evidence is available on effects occurring from exposures at sub-

31   daily averaging times?

- What do controlled human exposure, animal toxicologic, and epidemiologic studies indicate regarding the relationship between short-term exposures to CO and health effects of concern (e.g., reduced time to onset of angina pain) in healthy individuals and in those with preexisting disease states (e.g., individuals with cardiovascular disease)? What new evidence is available on effects occurring from exposures at sub-daily averaging times?

- What are the effects of CO exposure on respiratory gas-exchange surface in humans (e.g., oxygen diffusion capacity and ventilation-perfusion mismatches) and what is the potential clinical relevance of these effects?

- Is exposure to CO associated with mortality (total, respiratory or cardiovascular), hospital admissions, or emergency department visits as assessed using population-level datasets? What are the lowest ambient CO concentrations at which these associations are observed? What evidence is available to inform selection of the appropriate lag structure for specific health outcomes? The utility of the statistical methods applied will be evaluated (i.e., time-series studies). As discussed above, the potential effects of exposure error on epidemiologic outcomes will be evaluated.

- To what extent does exposure to CO contribute to health effects in the cardiovascular or other systems? What information can be obtained from electrocardiogram changes that may indicate an adverse response to CO? How does CO affect vascular and endothelial function and through which pathways?

- What is the impact of short-term exposures (days or less) on birth outcomes? Which gestational ages represent particularly vulnerable periods for the developing fetus?

- What is the nature of health effects in persons exposed to multipollutant mixtures that contain CO in comparison to exposure to CO alone?

- Does exposure to ambient CO perturb the biologic function of endogenous CO (e.g., by generating unwanted or excessive CO)? What are the effects of ambient and endogenous CO on oxidative stress and acute inflammation and other biological responses involved in pathophysiology?

1   ▪ What biomarkers of early effect may be used in the assessments? What detectable
2   biological changes will be considered adverse health effects?

3

4   Long-Term Exposure:

5   ▪ Does the scientific evidence support the occurrence of health effects from long-term
6   exposure (e.g., months to years) at ambient levels that are lower than previously
7   observed? If so, what uncertainties are related to these associations, and are the health
8   effects in question important from a public health perspective?

9   ▪ Can long-term exposures to CO result in chronic effects such as developmental effects
10   or birth outcome effects?

11   ▪ What are relevant exposure periods for effects associated with birth outcomes? What
12   metrics are appropriate for assessing developmental effects (e.g., low birth weight,
13   preterm birth)? Are certain effects linked to specific exposure windows?

14   ▪ To what extent does long-term CO exposure promote development of chronic
15   cardiovascular disease? What is the relationship between long-term CO exposure and
16   shortening of human life span via promotion of such diseases?

17   ▪ Are there annual and seasonal patterns of CO exposure that are associated with
18   potentially harmful health effects?

19

20   Causality: The ISA will evaluate the evidence for and against a causal relationship between
21   observed health outcomes and CO exposure. Biological plausibility and coherence of the
22   evidence will be key considerations in drawing conclusions about causality. The ISA will place
23   emphasis on studies conducted at or near typical ambient levels, except regarding evidence of
24   biological plausibility and mechanisms, as these may only be observable in animal or human
25   exposure study populations at higher levels than they might be observed in susceptible human
26   populations. The ISA will also assess any information available from "intervention" studies
27   regarding the health impacts of decreases in ambient levels of CO that is relevant to the
28   evaluation of causality in CO-health outcome relationships or benefits accruing from such
29   interventions.

1   ▪ Does the evidence base contain new information to evaluate the case for or against a

2   causal relationship between health effects and CO exposure?

3   ▪ What information is available regarding the health impacts of a decrease in ambient

4   levels of CO?

5   ▪ What insights can be gained regarding causality by comparing health effects observed

6   in older multipollutant studies (with comparatively higher ambient CO levels) with

7   more recent multipollutant studies?

8

9 Uncertainties: The ISA will evaluate uncertainty in the scientific data, particularly in relation to

10 observed epidemiologic findings and their consistency with toxicologic studies in terms of

11 observed effects and biological pathways.

12   ▪ How does confounding by coexposure to other pollutants (e.g., O_3, PM, SO_2, and NO_2)

13   and meteorological factors influence the associations observed with CO for both short-

14   and long-term exposures? The manner in which ambient CO concentration may serve

15   as a surrogate for exposure to vehicle exhaust pollutants, including gases and particles,

16   will be discussed.

17   ▪ What are the uncertainties due to other factors in epidemiologic studies (e.g.,

18   demographic and lifestyle attributes, genetic susceptibility factors, occupational

19   exposure, and medical care)?

20   ▪ What is the shape of the concentration-response model (e.g., linear vs. threshold

21   models) and associated community risks)?

22   ▪ What are the uncertainties associated with comparing the results of birth outcome

23   studies utilizing different study designs, metrics, and endpoints?

24   ▪ What uncertainties surround the evidence for long-term effects such as life shortening

25   and development/progression of disease?

26

27 Biological Mechanisms of Action: The ISA will evaluate the data examining mechanisms for

28 the health outcomes associated with exposure to CO.

- Is there new information related to the pathways and biological mechanism of action?

- What are the potential mechanisms of response to CO, with a focus on physical-chemical characteristics, response pathway(s), and exposure-dose-response relationships?

- What indicators other than carboxyhemoglobin (COHb) may be relevant for characterizing physiological effects of CO exposure (e.g., percent oxygen saturation)?

- What are the effects of age, gender, and pre-existing disease on cellular and tissue responses to CO-induced injury?

- What physiological characteristics of fetuses and neonates may lead to differential responses and effects compared to adults?

- Which CO-induced health effects are sufficiently characterized to be quantitatively compared across species?

- What are the interspecies differences in sensitivity to CO and in basic mechanisms of injury and repair? What are the implications of interspecies differences for extrapolation of results to humans?

- What is the state of knowledge of laboratory animal-to-man extrapolation of effects? Are credible qualitative and/or quantitative extrapolations possible for short- and for long-term exposures?

Susceptible Populations: The ISA will examine health outcome data to identify specific groups that are more susceptible to the adverse effects of CO exposure than normal healthy adults (e.g., patients with cardiovascular disease, COPD, persons with reduced or abnormal hemoglobin, older adults, fetuses, neonates). The host and environmental factors that are responsible for differential susceptibility to CO will be investigated.

- What do controlled human exposure, animal toxicologic, and epidemiologic studies indicate regarding the relationship between acute exposures to CO and health effects of concern in healthy individuals and in those individuals with preexisting diseases (e.g., cardiovascular diseases, COPD)? What other medical conditions or medications are identified as increasing susceptibility to CO effects? What are the pathways and

1   mechanisms through which CO may be acting for these groups? What is the nature

2   and time-course of the development of effects in healthy persons and in persons with

3   preexisting disease?

4   ▪ Is preexisting respiratory or cardiovascular disease in conjunction with advanced age

5   an important factor in susceptibility to mortality associated with exposure to CO?

6   ▪ Regarding morbidity health endpoints, to what extent are older adults and fetuses more

7   sensitive than the general population to CO exposure?

8   ▪ How should sensitive subpopulations be considered in interpretation of

9   epidemiological results and exposure-response characteristics, considering that these

10   results may be driven by the more sensitive subpopulations?

11   ▪ Is susceptibility to the effects of short-term CO exposure associated with long-term CO

12   susceptibility?

13   ▪ What host and environmental factors (e.g., demographic, socioeconomic, and genetic)

14   are associated with susceptibility to short- and long-term exposure to CO?

15

16   Public Health Impact: The ISA will present concepts related to the potential for defining adverse

17   health effects. To accomplish this, the implications for public health of different health effects

18   will be discussed. This will include, as appropriate, an estimation of the potential number of

19   persons at risk in specific at-risk population groups. The concept of attributable risk, which

20   considers the exposure of a subpopulation along with relative risk, will be evaluated in

21   consideration of the public health impact. Low-level effects will be interpreted in light of the

22   policy-relevant background concentration of CO. Furthermore, the analysis will identify and

23   address, as appropriate, disproportionately high and adverse human health or environmental

24   effects of CO on minority populations and low-income populations.

25

26   **Annexes to the ISA**

27   The ISA will be supplemented by a series of annexes, which will be focused on

28   accomplishing two goals. The first goal will be to identify scientific research that is relevant to

29   informing key policy issues. The second goal will be to produce a base of evidence containing

1   all of the publications relevant to the CO review. The annexes will provide information on (1)

2   the chemistry, physics, sources, and emissions of CO, as well as sampling and analytic methods

3   for measurement of CO; 2) environmental concentrations and human exposure to CO; (3)

4   dosimetry; (4) toxicologic studies of CO health effects in laboratory animals and in vitro

5   systems; (5) human clinical studies examining health effects following controlled exposure to

6   CO; and (6) epidemiologic studies of health effects from short- and long-term exposure to CO.

7   More detailed information on various methods and results for the health studies will be

8   summarized in tabular form in the annexes. These tables will generally be organized to include

9   information about (1) concentrations of CO levels and averaging times; (2) description of study

10   methods employed; (3) results and comments; and (4) quantitative outcomes for CO measures.

11   Additionally, annexes will contain background material on legislative requirements, the NAAQS

12   review process, and the history of earlier CO reviews.

13
14

15 **4.3   SCIENTIFIC AND PUBLIC REVIEW**

16   Drafts of the ISA will be reviewed by the CASAC CO Review Panel of EPA's Science

17   Advisory Board (SAB) and made available for public comment. The annexes to the ISA will

18   also be made available to CASAC in order to assist with their review; however, CASAC

19   members will not be specifically charged with reviewing the annexes. The CASAC CO Review

20   Panel will review the first draft ISA and discuss their comments in a public meeting announced

21   in the Federal Register. Based on CASAC's past practice, EPA expects that the CASAC chair

22   will summarize key CASAC advice and recommendations for revision of the document in a

23   letter to the EPA Administrator. In revising the first draft ISA for CO, EPA will take into

24   account any such recommendations. EPA will also consider comments received, from CASAC

25   or from the public, at the meeting itself and any written comments received. EPA will prepare a

26   second draft ISA for CASAC review and public comment. The CASAC CO Review Panel will

27   review the second draft ISA and discuss their comments in a public meeting announced in the

28   Federal Register. Again, based on CASAC's past practice, EPA anticipates the CASAC chair

29   will summarize key advice and recommendations for revision of the second draft ISA in a letter

30   to the EPA Administrator. In finalizing the ISA, EPA will take into account any such

31   recommendations. EPA will also consider comments received from CASAC or from the public

1   at the meeting itself and any written public comments. After appropriate revision, the final

2   document will be made publicly available on an EPA website and in hard copy. A notice

3   announcing the availability of the final ISA will be published in the Federal Register. In

4   addition, the final ISA will be placed in the rulemaking docket.

5

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5. RISK/EXPOSURE ASSESSMENT

5.1 SCOPE AND ORGANIZATION

The risk/exposure assessments for the current review of the primary CO NAAQS will be designed to estimate human exposures and to characterize the potential health risks that are associated with current ambient levels, with ambient levels that just meet the existing standard, and with ambient levels that just meet alternative standards that may be under consideration. The risk/exposure assessments will draw upon the information presented in the ISA and its Annexes. This includes information on atmospheric chemistry, air quality, human exposure, formation of COHb levels, and health effects of concern. In particular, the availability of concentration-response and dose-response data from the health effects literature will influence the type of risk and exposure assessments that would be performed.

The assessments will focus on exposures and dose metrics that are consistent with health effects of concern and will be enhanced with available measurement and modeled data, where appropriate, to generate the best possible estimates of exposure. These estimates will then serve as a measure of comparison to identified health benchmarks to (1) estimate the number of individuals at risk of experiencing exposures of concern, and (2) estimate the magnitude of exposures above levels of concern. The components of the exposure/risk assessments are outlined below and will be described in detail in the Scope and Methods Plan. The Scope and Methods Plan will be the subject of a consultation with the CASAC CO Panel and will be made available to the public for review and comment. The draft risk/exposure assessments prepared based on the Scope and Methods Plan will be made final upon completion of the final ISA for CO and following review by the CASAC CO Primary Review Panel and the public.

5.2 OVERVIEW OF PREVIOUS EXPOSURE ASSESSMENTS

1992 Exposure Analysis for Denver, Colorado

In the previous review of the NAAQS for CO, a quantitative analysis of CO exposures in Denver, CO, was conducted to provide estimates of CO exposure and their resultant COHb levels for people living in one city for different exposure scenarios. The analysis provided a

1   basis for assessing protection afforded by the current CO standards and preliminary insight into

2   the relative impact of certain indoor sources to total CO exposure. Denver was chosen because

3   (1) in 1988 it violated both the current 1-hour and 8-hour CO NAAQS (one of only two areas

4   that exceeded both standards at the time); (2) it had a relatively high 8-hour design value, 16.2

5   ppm--the second-highest design value in the U.S. at the time; and (3) CO personal monitoring

6   data were available for a rough validity check of the modeling effort. Four scenarios were

7   modeled that provided insight into exposures related to (1) current air quality versus future air

8   quality associated with just meeting the 8-hour CO NAAQS and (2) common indoor sources

9   present versus ambient air without these indoor sources. Only the 8-hour NAAQS was evaluated

10   since previous analyses indicate that it is the controlling standard (US EPA, 1979b). Indoor

11   sources that were considered included residential gas stoves and passive smoking. Other indoor

12   sources, such as running automobiles in private or public garages and CO intrusion into a motor

13   vehicle from the vehicle itself, were not included in any of the scenarios.

14   The model used for exposure analysis was pNEM/CO (probabilistic NEM applied to

15   CO), a version of the CO NAAQS Exposure Model (NEM) that incorporated Monte Carlo

16   sampling and multiple runs, or realizations, of the model. The major model outputs of interest

17   were estimates of the number of person-days of exposure to various CO levels for the four

18   scenarios mentioned above for adults with cardiovascular disease in Denver. In addition,

19   estimates also were made of the percentage of the cardiovascular heart disease population in

20   Denver that would exceed selected COHb levels one or more times per year under the four

21   scenarios. The estimates of COHb were derived by applying a modified version of the Coburn

22   Forster Kane (CFK) differential equation that estimates COHb levels from CO exposure as a

23   function of time and physiological and environmental factors (e.g., blood volume, altitude,

24   endogenous CO production rate). It was estimated at the time that there were about 36,800 non-

25   smoking adults in Denver with diagnosed or undiagnosed (silent) ischemia.

26   The analysis indicated that if the current 8-hour standard were just met, the proportion of

27   the nonsmoking population with cardiovascular disease experiencing exposures at or above 9

28   ppm for 8 hours decreased by an order of magnitude or more, down to less than 1 percent of the

29   total person-days in that population. Likewise, meeting the current 8-hour standard reduced the

30   proportion of the nonsmoking cardiovascular-disease population person days at or above COHb

31   levels of concern by an order of magnitude or more. Upon meeting the 8-hour standard, EPA

1   estimated that less than 0.1 percent of the nonsmoking cardiovascular-disease population would

2   experience a COHb level of about 2.1 percent. A smaller population was estimated to exceed

3   higher COHb percentages. Based on this assessment, and considering the 1985 review of similar

4   CO effects and effects levels, the Administrator concluded that the evaluation of adequacy of the

5   existing CO standards should focus on reducing the number of individuals with cardiovascular

6   disease from being exposed to CO levels in the ambient air that would result in COHb levels of

7   2.1 percent or greater. The Administrator concluded that standards that protect against COHb

8   levels at the lower end of the range would provide an adequate margin of safety against effects of

9   uncertain occurrence, as well as those of clear concern that have been associated with COHb

10   levels in the upper-end of the range. The Administrator also concluded that relatively few people

11   of the cardiovascular sensitive population group analyzed would experience COHb levels ≥ 2.1

12   percent when exposed to CO levels in the absence of indoor sources when the current ambient

13   standards are attained. The analysis also indicated, however, that certain indoor sources (e.g.,

14   passive smoking, gas stove usage) contributed to total CO exposure but could not be effectively

15   mitigated by ambient air quality standards.

16   The 8-hour standard was chosen because most individuals, even at rest, appeared to

17   approach equilibrium levels of COHb after 8 hours of exposure. In addition the 8-hour period

18   approximated blocks of time for which people are often exposed in a particular location or

19   activity (e.g., sleeping, working) and provided a good indicator for tracking continuous

20   exposures that occurred during any 24-hour period. The 1-hour standard was chosen because a

21   1-hour averaging period provided a better indicator of short-term health effects of CO and a 1-

22   hour standard provided reasonable protection from effects that might be encountered from very

23   short duration peak exposures in the urban environment. Review of scientific information in the

24   1991 Criteria Document indicated that these reasons for choosing averaging times for the CO

25   standards remained valid and there were no compelling arguments for selecting new or different

26   averaging times. The Administrator also considered and concurred with the staff

27   recommendations contained in the 1992 Staff Paper that both averaging times should be

28   retained for the primary CO standards. For the above reasons, the Administrator determined

29   under section 109(d)(1) that revisions of the 1-hour (35 ppm) and 8-hour (9 ppm) primary

30   standards for CO were not appropriate at that time.

31

1   **1999 Exposure Analysis for Denver**

2   Additional exposure analyses were planned in 1999 using the Denver and Los Angeles

3   (LA) areas to provide estimates of CO exposures and resultant COHb levels for adults in two

4   urban areas. Denver was included in the planned analyses for comparison purposes because it

5   was the only city included in the exposure analysis conducted in the previous review. In

6   addition, Denver was one of a few areas where a personal CO exposure study had been

7   conducted. After an initial review of the methodology, EPA planned to also conduct the

8   analyses for LA for several reasons: (1) it presented the largest potential public health burden

9   due to its ambient CO levels and potential population exposure; (2) an extensive monitoring

10   network was available; and (3) an existing study of personal and indoor CO concentrations that

11   potentially could be used to evaluate the model had been conducted in Los Angeles.   The

12   primary target population was adults with cardiovascular disease, as it was in the 1992 analysis.

13   The 1999 analysis initially focused on several scenarios: (1) current air quality (1995 for

14   Denver); and (2) the presence of indoor sources (gas stoves/ovens and passive smoking) versus

15   ambient air without indoor sources. The analyses were intended to provide a basis for assessing

16   protection afforded by the current CO standards and preliminary insight into the relative impact

17   indoor sources may have on total exposure. The model selected to estimate population exposure

18   was an updated version of pNEM/CO that was used in the 1992 Denver analysis, with the major

19   outputs of interest being estimates of the number and percentage of person-days of exposure to

20   various CO levels and the number and percentage of person-hours and people exceeding various

21   COHb levels. Only the 8-hour NAAQS was planned for evaluation because previous analyses

22   indicated that it was the controlling standard for attainment.

23   A draft exposure analysis report (Johnson et al, 1999) applying the updated exposure

24   model only to the Denver area was provided to the CASAC CO Panel and made available for

25   public review in March 1999 for the purpose of obtaining scientific and public input on the

26   proposed methodology. The CASAC CO Panel conducted a consultation on the methodology

27   for the analysis on June 9-10, 1999. The CO NAAQS review was put on hold, however, and the

28   exposure analysis was not completed. For this current review, EPA staff will build upon the

29   1999 work and subsequent improvements to the exposure model (now called APEX) in

30   developing its plan for CO exposure assessment.

31

5.3   EXPOSURE ASSESSMENT APPROACH

The exposure assessment approach for the current review will be informed by the previous reviews of the AQCDs for CO (US EPA, 1991, 2000), recent guidelines from the World Health Organization (2006), and information contained within the ISA and relevant Annexes. The goals of the CO exposure assessment are: (1) to identify locations where current ambient concentrations exceed health benchmarks of concern, (2) to estimate the number of people exposed to CO concentrations of concern considering current air quality and just meeting alternative CO standards; (3) to provide distributions of exposure estimates over the entire range of ambient CO concentrations for use in assessing populations at risk; (4) to develop estimates of COHb levels in sensitive populations resulting from different CO exposure scenarios; and (5) to identify key assumptions and uncertainties in the exposure estimates.

Air Quality Characterization

The first step in assessing exposure will be to conduct an air quality analysis relying largely on ambient air quality data and the information provided in the ISA and relevant Annexes. This analysis will include information on CO properties, current CO air quality patterns, historic trends, policy-relevant background levels[6], and exposure/dose levels of concern. This analysis will provide a frame of reference for subsequent discussions of current and possible alternative standards. General steps in the process include the following.

- Obtain ambient monitoring data collected since the prior NAAQS review (e.g., 1995-2007)
- Estimate number of exceedances (if any) of the current CO standards using recent monitoring data (e.g., years 2003-2007)
- Estimate number of exceedances of several short-term peak air quality indicators (e.g., 1-hour exceedances greater than 35 ppm and 8-hour exceedances greater than 9 ppm) given attainment of the current CO standards and potential alternative standards (using all available data).
- Identify individual locations to evaluate, such Los Angeles, Houston, Phoenix, New York, or other Combined Statistical Areas (CSAs) that may contain higher than

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6 Policy-relevant background is defined as the distribution of CO concentrations that would be observed in the U.S. in the absence of anthropogenic (man-made) emissions of CO in the U.S., Canada, and Mexico.

1   average number of peak concentrations. Criteria will be developed for selection of

2   appropriate areas and groupings based on statistical comparisons of ambient

3   concentrations and the influence on ambient concentrations by local sources of CO

4   (e.g., motor vehicle traffic).

5   ▪ Develop methods to adjust recent CO air quality data to simulate just meeting the

6   current standards and any alternative CO standards. EPA will consider alternative air

7   quality simulation procedures, including a proportional rollback procedure, for use in

8   this current review. EPA will also evaluate candidate procedures for simulating

9   changes in CO air quality likely to result from just meeting the current or alternative

10   standards based on analyzing changes in CO levels that observed historically and/or

11   analyzing changes in CO levels predicted by air quality models. EPA will consider

12   factors which may influence the concentration distributions such as potential source

13   contributions, as well as the influence of local and regional pollution. In this review,

14   EPA also will examine current techniques that may be used to assess the variability

15   and uncertainty of the simulated change in concentrations likely to result from just

16   meeting the current or alternative standards.

17   ▪ Evaluate the relationship between 1-hour and 8-hour peak concentrations across

18   multiple years using locations and groupings identified above.

19

20   **Exposure Assessment**

21   The general approach would be to estimate population exposures to ambient CO in a

22   number of urban areas across the U.S. identified above, and possibly including a rural area

23   (generally not impacted greatly by mobile sources) as a reference group for the analysis. Areas

24   included in the analysis would be selected with the goal of achieving variation in population,

25   geography, demographics, climate, and CO air quality. Exposure estimates would be generated

26   for current CO levels, for levels assuming just meeting the current NAAQS, and for levels

27   assuming attainment of potential alternative standards.

28   The exposure assessment would take into account several important factors including the

29   magnitude and duration of exposures, frequency of repeated high exposures, and breathing rate

30   of individuals at the time of exposure. Estimates would be developed for multiple indicators of

31   exposure including (1) counts of people exposed one or more times to a given CO concentration

1   while at a specified breathing rate and (2) counts of person-occurrences of particular exposures,

2   which accumulate across all people in the population of interest.

3   EPA's Air Pollutants Exposure (APEX) model (also referred to as the Total Risk

4   Integrated Methodology/Exposure (TRIM.Expo) model) would be used in this analysis. APEX

5   is a Monte Carlo simulation model that can be used to simulate a large number of randomly

6   sampled individuals within each area thus generating area-wide estimates of population

7   exposure. APEX simulates exposures in indoor, outdoor, and in-vehicle microenvironments

8   while taking into consideration the movement of individuals through time and space. A user's

9   guide and technical support document describe the APEX model in detail (U.S. EPA 2006 a,b).

10

11 **5.4   RISK ASSESSMENT APPROACH**

12   A two-tiered approach to characterizing health risks will be employed. In a first tier

13 analysis, potential health effect benchmarks that may be identified based on information in the

14 ISA would be combined with exposure or dose estimates from the exposure/dose assessment in

15 order to characterize population health risks. In a second tier risk analysis, which would be

16 conducted only if judged appropriate and if relevant data are available, an assessment using

17 concentration-response or exposure/dose-response data would be conducted by combining this

18 data with either ambient distributions or estimated exposure or dose distributions, respectively.

19   The goals of a CO risk assessment would be: (1) to estimate the number of people

20 exposed to CO concentrations or COHb levels above health effects benchmarks considering

21 current air quality and air quality levels simulated to just meet the current and potential

22 alternative CO standards; (2) to provide distributions of health risk estimates over a range of

23 ambient CO concentrations; and (3) to identify key assumptions and uncertainties in the risk

24 estimates.

25   Risks would also be characterized using a tiered approach where progression to a more

26 sophisticated level of analysis would depend on the availability of data and on the anticipated

27 utility of the results. For example, risks could be assessed through the identification of exposure

28 or COHb levels anticipated to result in adverse health effects, termed health effect benchmarks.

29 These health effect benchmarks could then be used to determine how often air quality

30 concentrations or estimated exposures or COHb levels exceed benchmarks associated with

31 adverse health effects. Concentration-response functions, derived from epidemiologic studies,

1   and/or dose-response functions, derived from human clinical studies, may also be combined with

2   estimated exposures and/or doses to characterize CO health risk as appropriate and to the extent

3   such information is available.

4

5   **Health Effect Benchmarks**

6   This type of risk characterization would use exposure and/or dose (i.e., COHb) estimates,

7   along with potential health effect benchmarks that may be identified based on information in the

8   ISA and relevant Annexes, to estimate (1) the number of individuals with exposures above levels

9   expected to cause adverse health effects, and (2) the percent of at risk populations experiencing

10   exposures and/or dose levels of concern. Multiple exposure scenarios will be considered,

11   including exposure associated with current ambient air quality, with current air quality levels

12   enhanced by including local source contributions, and/or with levels of CO associated with

13   simulating just meeting the current and potential alternative standards. The health effect

14   benchmarks will account for those individuals who are particularly susceptible and/or vulnerable

15   to the effects of CO (e.g., cardiopulmonary disease populations). The health risk

16   characterization would require that averaging times be comparable for any estimated exposure

17   concentrations and health metrics. For the purposes of this assessment, the approach is similar to

18   calculating a hazard quotient which is the ratio of a weighted population exposure (or individuals

19   in the case of a refined exposure assessment) to a health benchmark concentration.

20

21   **Exposure-Response and Concentration-Response Functions**

22   Incorporating dose-response or concentration-response data into the risk characterization

23   will depend on the availability of data from controlled human exposure studies and

24   epidemiologic studies, respectively. In either case, quantitative relationships provided by studies

25   or derived from the data presented in studies describe the change in concentration (either ambient

26   or exposure) or dose (COHb level) associated with a change in health response. These

27   relationships are applied to estimate health risk.

28   Controlled human exposure studies involve volunteer subjects who are exposed to

29   specified levels of CO under controlled conditions for specified lengths of time. The endpoints

30   of interest in previous reviews were related to the cardiovascular and central nervous systems,

31   including decrement in time to onset of chest pain and ST segment suppression in patients with

1   angina pectoris, reduced maximal exercise duration in healthy adults due to decreased oxygen

2   uptake, increased number and complexity of arrhythmia in individuals with chronic arrhythmia,

3   and short-term effects on hand-eye coordination and vigilance in healthy individuals. These

4   responses formed the basis for the development of health benchmarks related to specified COHb

5   levels.

6   In contrast, epidemiological studies typically provide estimated concentration-response

7   (C-R) relationships based on data collected in environmentally-relevant settings. Ambient CO

8   concentration is typically included in health effects models as the average of monitor-specific

9   measurements. Common health responses that have been evaluated for CO include

10 developmental effects, as well as cardiac and respiratory morbidity and mortality, although in the

11 previous review the epidemiologic evidence was plagued with inconsistencies. Again,

12 depending on the type of health response function(s) available, ambient CO concentration data

13 might be used for characterizing risks, and are most appropriately applied in the geographic area

14 where the epidemiological study was performed. It should be noted that a risk characterization

15 based on epidemiological studies also requires baseline incidence rates and population data for

16 the risk assessment locations.

17   Based on our current understanding of the available evidence, we do not anticipate that

18 there will be sufficient exposure- or dose-response data from controlled human exposure studies

19 to characterize health risks in this manner. However, there may be limited data available to

20 develop C-R relationships from recently conducted epidemiologic studies. Following review of

21 the draft ISA and considering comments and recommendations from CASAC, the risk/exposure

22 assessment scope and methods plan will be designed to include such a proposed approach to

23 characterizing health risk if warranted.

24

25 **5.5   ASSESSMENT CRITERIA**

26   Criteria will be established to determine the level of detail warranted and the specific

27 design of the assessments. The criteria will be designed to determine the value added to the

28 assessment as measured by the reduction of uncertainties in the exposure and risk estimates. In

29 order to determine which level of detail is warranted, the following factors will be considered by

30 the workgroup and EPA management:

1   ▪ Results of the ambient air quality indicator analysis;

2   ▪ Weight-of-evidence, as provided in the ISA, from new controlled human exposure

3   studies with relevant exposure-response data, particularly those conducted at or near

4   current ambient concentrations;

5   ▪ Weight-of-evidence, as provided in the ISA, from new epidemiological studies that

6   evaluate the relationship between short-term repeated peak exposures and health

7   outcomes;

8   ▪ New information regarding susceptible populations identified in previous reviews

9   (e.g., those with pre-existing cardiovascular disease) or information regarding newly

10   identified susceptible populations;

11   ▪ Information and data defining the potential impact of roadway CO concentrations on

12   nearby residents and on specific microenvironmental concentrations (e.g., while

13   traveling inside motor vehicles);

14   ▪ Analysis of exposure studies using non-routine monitoring, other local sources (e.g.,

15   rail-yards, airports), and/or modeled CO concentrations;

16   ▪ Existence of the data required to perform the analyses in each stage of the assessment.

17

5.6 UNCERTAINTY AND VARIABILITY

19   The uncertainty and variability inherent in estimates of exposure and risk will be

20 characterized regardless of the type of risk and exposure assessment conducted. Uncertainty

21 reflects the degree of confidence in the representativeness of models or model components.

22 Variability can be described in terms of empirical quantities that are inherently variable across

23 time and space or between individuals (Cullen and Frey, 1999).

24   Assessing uncertainty and variability will begin with a qualitative analysis and progress

25 to a quantitative analysis if data are available to support such an analysis. The first step in the

26 uncertainty analysis will be to identify the components of the assessment, determine whether

27 uncertainty can be evaluated for each of those components, and provide a rationale for why this

28 is the case. The second step will be to perform a qualitative uncertainty analysis for the

29 appropriate components of the assessment. This qualitative analysis will result in a matrix

30 describing, for each area of uncertainty, both the magnitude (minimal, moderate, major) and the

31 direction of influence (under- or over-estimate) on risk/exposure estimates. If sufficient data are

1 available, and if the magnitude of uncertainty is judged significant, a quantitative assessment of

2 uncertainty will then be performed for selected components of the assessment.

3   There are two primary sources of uncertainty that would be addressed in a quantitative

4 analysis. The first is uncertainty associated with the model inputs (e.g., use of air quality data,

5 time-location-activity diaries, microenvironmental factor distributions). The second is

6 uncertainty associated with model formulation (e.g., algorithms included in the model). Each of

7 these is described below in more detail.

8   APEX is a Monte Carlo simulation model that explicitly incorporates the variability

9 inherent in the model input data. A 2-dimensional Monte Carlo Latin hypercube sampling

10 approach could be used as a combined variability and uncertainty analysis for APEX. A Monte

11 Carlo approach entails performing a large number of model runs with inputs randomly sampled

12 from specified distributions that reflect the variability and uncertainty of the model inputs. The

13 2-dimensional Monte Carlo method allows for the separate characterization of variability and

14 uncertainty in the model results (Morgan and Henrion, 1990). If this approach were taken,

15 developing appropriate distributions representing both variability and uncertainty in model inputs

16 (e.g., air exchange rates, CO decay rates, physiological parameters) would be a key part of the

17 effort.

18   In the case of model formulation, the preferred approach would be to compare model

19 estimates with measured values, while having relatively complete knowledge of the uncertainty

20 associated with input parameters. For the purpose of the exposure assessment, model estimated

21 exposures would be compared with measured personal exposures, provided appropriate data

22 exist (e.g., similar averaging times, population demographics, geographic locations). In the

23 absence of measurements that can be used to estimate model uncertainty, the analysis must rely

24 on informed judgment. The approach would be to partition the model formulation uncertainty

25 into that of the components, or sub-models, of APEX (e.g., microenvironemental concentrations,

26 ventilation estimates). For each of the sub-models, we would discuss the simplifying

27 assumptions and the uncertainties associated with those assumptions. Where possible, we would

28 evaluate these sub-models by comparing their predictions with measured data. Where this is not

29 possible, we would formulate an informed judgment regarding a range of plausible uncertainties

30 for the sub-models.

31

1

5.7   PUBLIC AND SCIENTIFIC REVIEW

2

3   The CASAC CO Panel will be consulted on the assessment approach at a public meeting.

4   Drafts of the exposure analysis will also be reviewed by CASAC. CASAC members and

5   consultants will review the draft document and discuss their comments in a public meeting

6   announced in the Federal Register. Based on CASAC's past practice, EPA expects that key

7   CASAC advice and recommendations for revision of the document will be summarized by the

8   CASAC Chair in a letter to the EPA Administrator. In revising the draft exposure analysis for

9   CO, EPA will take into account any such recommendations. EPA will also consider comments

10 received, from CASAC or from the public, at the meeting itself and any written comments

11 received. EPA anticipates preparing a second draft of the exposure analysis for CASAC review

12 and public comment. After appropriate revision, the final document will be made available on

13 an EPA website and subsequently printed, with its public availability being announced in the

14 Federal Register.

15

16

6. POLICY ASSESSMENT/RULEMAKING

Based on the information in the ISA and the exposure assessment report, the Agency will develop an ANPR that reflects EPA's views regarding the need to retain or revise the NAAQS for CO. The ANPR will identify conceptual evidence-based and exposure/risk-based approaches for reaching public health policy judgments. It will also discuss the implications of the science and exposure/risk assessments for the adequacy of the current standards, and for consideration of alternative standards. The ANPR will also describe a range of policy options for standard setting including a description of the underlying interpretations of the scientific evidence and risk/exposure information that might support such alternative standards and that could be considered by the Administrator in making NAAQS decisions.

The final decision to retain or revise the NAAQS is a public health policy judgment. A final decision should draw upon scientific information and analyses related to health effects, population exposure and risks, and judgments about the appropriate response to the range of uncertainties that are inherent in the scientific evidence and analyses. The Agency's approach to informing these judgments is based on a recognition that the available health effects evidence generally reflects a continuum consisting of ambient levels at which scientists generally agree that health effects are likely to occur through lower levels at which the likelihood and magnitude of the response become increasingly uncertain. The ANPR will help to bridge the gap between the Agency's scientific assessment and the judgments required of the Administrator in determining whether it is appropriate to retain or revise the standards.

Publication of the ANPR will provide an opportunity for CASAC and the public to evaluate the policy options under consideration and to offer comments and recommendations to inform the development of a proposed action. The Agency will also solicit public comment on the proposed action in order to inform the final decision. Issuance of a final decision will complete the rulemaking process.

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