Plan for Review of the National Ambient Air Quality Standards 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 changes in the court-ordered schedule or information developed during this review, including advice and comments received from the Clean Air Scientific Advisory Committee and the public. 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 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 standards: the indicator, averaging time, form, and level. These elements, which serve to define each ambient air quality standard, must be considered collectively in evaluating the degree of 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. There is currently no secondary standard for CO.

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/). This new process, which is being applied to the current review of the NAAQS for CO, contains four major components: an integrated review plan, a science assessment, a risk/exposure assessment, and a policy assessment/rulemaking. Each of these components is described in this section.

[1] This plan will generally refer to the review of the primary standards 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.

The review process starts with the development of an integrated review plan prepared jointly by EPA's National Center for Environmental Assessment (NCEA), within the Office of Research and Development (ORD), and EPA's Office of Air Quality Planning and Standards (OAQPS), within the Office of Air and Radiation (OAR). This document represents the current plan and specifies the schedule for the entire review, the process for conducting the review, and the key policy-relevant science issues that will guide the review.

The second component of the review process is the development of the science assessment, which consists of an Integrated Science Assessment (ISA) and supporting annexes. NCEA collaborates with contracted expert support to prepare these documents. The annexes will contain a comprehensive description of the full breadth of the current scientific literature pertaining to known and anticipated effects on public health and welfare associated with CO in the ambient air, emphasizing the information that has become available since the last review in order to reflect the current state of knowledge. The annexes also provide in-depth treatment of specific topics supporting interpretation of health and welfare effects. NCEA will critically evaluate, integrate, and synthesize the most policy-relevant science into an ISA. The ISA is intended to provide information useful in forming judgments about air quality indicator(s), form(s), averaging time(s) and level(s) for the CO NAAQS. Hence, the ISA and its associated annexes function in the new NAAQS review as the Air Quality Criteria Document (AQCD) did in previous reviews. The schedule includes production of a first and second draft ISA, both of which will undergo CASAC and public review prior to completion of the final ISA. Section 4 provides a more detailed description of the planned scope, organization and assessment approach for the annexes and ISA.

In the third component of the revised review process, the risk/exposure assessment, EPA's Office of Air Quality Planning and Standards (OAQPS) plans to draw upon the information presented in the ISA to develop quantitative or qualitative estimates of the exposures and risks of adverse health effects associated with current ambient levels of CO, with levels that just meet the current standards, and with levels that just meet possible alternative standards. Section 5 of this integrated plan contains more detail about possible approaches EPA could take in conducting the human health assessments. Once the first draft ISA is complete, EPA will release a draft Scope and Methods Plan for human health assessments that CASAC and the public will review. The Scope and Methods Plan will describe the planned scope of the analyses to be performed and the

tools/methods that may be employed. Comments on the draft Scope and Methods Plan will be considered as EPA performs the actual analyses. The schedule includes production of first and second draft risk/exposure assessments, all of which will undergo CASAC and public review prior to completion of the final risk/exposure assessment reports that will focus on key results, observations, and uncertainties.

The fourth component of the revised process will be a policy assessment/rulemaking. Under the new process, a staff paper, such as that prepared in previous NAAQS reviews, will not be prepared. Rather, Agency views on policy options will be published in the Federal Register as part of a notice of proposed action, to be followed by a public comment period.[2] Considering comments received on the proposed action, the Agency will issue a final decision to complete the review.

1.2 LEGISLATIVE REQUIREMENTS

Two sections of the Clean Air Act (CAA) govern the establishment and revision of the NAAQS. Section 108 (42 U.S.C. 7408) directs the Administrator to identify and list air pollutants that "in his judgment, cause or contribute to air pollution which may reasonably be anticipated to endanger public health and welfare" and whose "presence . . . in the ambient air results from numerous or diverse mobile or stationary sources" and to issue air quality criteria for those that are listed. Air quality criteria are intended to "accurately reflect the latest scientific knowledge useful in indicating the kind and extent of identifiable effects on public health or welfare which may be expected from the presence of [a] pollutant in ambient air . . . ."

Section 109 (42 U.S.C. 7409) directs the Administrator to propose and promulgate "primary" and "secondary" NAAQS for pollutants listed under section 108. Section 109(b)(1) defines a primary standard as one "the attainment and maintenance of which in the judgment of the Administrator, based on such criteria and allowing an adequate margin of safety, are requisite to protect the public health."[3] A secondary standard, as defined in section 109(b)(2), must "specify a level of air quality the attainment and maintenance of which, in the judgment of the

[2] In addition, EPA is considering whether, and at what point in the process, to issue an Advance Notice of Proposed Rulemaking prior to the proposal notice.

[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

Administrator, based on such criteria, is requisite to protect the public welfare from any known or anticipated adverse effects associated with the presence of [the] pollutant in the ambient air."[4]

The requirement that primary standards include an adequate margin of safety was intended to address uncertainties associated with inconclusive scientific and technical information available at the time of standard setting. It was also intended to provide a reasonable degree of protection against hazards that research has not yet identified. See *Lead Industries Association v. EPA*, 647 F.2d 1130, 1154 (D.C. Cir 1980), *cert. denied*, 449 U.S. 1042 (1980); *American Petroleum Institute v. Costle*, 665 F.2d 1176, 1186 (D.C. Cir. 1981), *cert. denied*, 455 U.S. 1034 (1982). Both kinds of uncertainties are components of the risk associated with pollution at levels below those at which human health effects can be said to occur with reasonable scientific certainty. Thus, in selecting primary standards that include an adequate margin of safety, the Administrator is seeking not only to prevent pollution levels that have been demonstrated to be harmful but also to prevent lower pollutant levels that may pose an unacceptable risk of harm, even if the risk is not precisely identified as to nature or degree.

In selecting a margin of safety, the EPA considers such factors as the nature and severity of the health effects involved, the size of sensitive population(s) at risk, and the kind and degree of the uncertainties that must be addressed. The selection of any particular approach to providing an adequate margin of safety is a policy choice left specifically to the Administrator's judgment. See *Lead Industries Association v. EPA*, 647 F.2d at 1161-62.

In setting standards that are "requisite" to protect public health and welfare, as provided in section 109(b), EPA's task is to establish standards that are neither more nor less stringent than necessary for these purposes. In so doing, EPA may not consider the costs of implementing the standards. See generally, *Whitman v. American Trucking Associations*, 531 U.S. 457, 465-472, 475-76 (2001).

Section 109(d)(1) requires that "not later than December 31, 1980, and at 5-year intervals thereafter, the Administrator shall complete a thorough review of the criteria

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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."

published under section 108 and the national ambient air quality standards . . . and shall make such revisions in such criteria and standards and promulgate such new standards as may be appropriate . . . ." Section 109(d)(2) requires that an independent scientific review committee "shall complete a review of the criteria . . . and the national primary and secondary ambient air quality standards . . . and shall recommend to the Administrator any new . . . standards and revisions of existing criteria and standards as may be appropriate . . . ." Since the early 1980's, this independent review function has been performed by the Clean Air Scientific Advisory Committee (CASAC) of EPA's Science Advisory Board.[5]

1.3 HISTORY OF REVIEWS OF THE NAAQS FOR CO

On April 30, 1971, EPA promulgated identical primary and secondary NAAQS for CO, under section 109 of the Act, set at 9 parts per million (ppm), 8-hour average and 35 ppm, 1-hour average, neither to be exceeded more than once per year (36 FR 8186). In 1979, EPA published *Air Quality Criteria Document for Carbon Monoxide* (AQCD) (US EPA, 1979a), which updated the scientific criteria upon which the initial CO standards were based. A Staff Paper (US EPA, 1979b) was prepared and, along with the AQCD, served as the basis for development of proposed rulemaking (45 FR 55066) published on August 18, 1980. Delays due to uncertainties regarding the scientific basis for the final decision resulted in EPA's announcing a second public comment period (47 FR 26407). Following substantial reexamination of the scientific data, EPA prepared an Addendum to the 1979 AQCD (EPA, 1984a) and an updated Staff Paper (US EPA, 1984b). Following review by CASAC, EPA announced its final decision (50 FR 37484) not to revise the existing primary standard and to revoke the secondary standard for CO on September 13, 1985, due to a lack of evidence of direct effects on public welfare at ambient concentrations.

In 1987, EPA initiated action to revise the criteria for CO and released a revised AQCD for CASAC and public review. In a "closure letter" (McClellan, 1991) sent to the Administrator, the CASAC concluded that the AQCD (US EPA, 1991) ". . . provides a scientifically balanced and defensible summary of current knowledge of the effects of this pollutant and provides an adequate basis for the EPA to make a decision as to the appropriate primary NAAQS for CO." A revised Staff Paper subsequently was reviewed by CASAC and the public, and in a "closure

[5] See http://yosemite.epa.gov/sab/sabproduct.nsf/WebCASAC/CommitteesandMembership?OpenDocument for a list of members of CASAC and of the CASAC CO Review Panel.

letter" (McClellan, 1992) sent to the Administrator, it was stated ". . . that a standard of the present form and with a numerical value similar to that of the present standard would be supported by the present scientific data on health effects of exposure to carbon monoxide." Based on the revised AQCD (US EPA, 1991) and staff conclusions and recommendations contained in the revised Staff Paper (US EPA. 1992), the Administrator announced the final decision (59 FR 38906) on August 1, 1994, that revision of the primary NAAQS for CO was not appropriate.

In 1997, revisions to the AQCD were initiated. A workshop was held in September 1998 to review and discuss material contained in the revised AQCD. On June 9, 1999, CASAC held a public meeting to review the draft AQCD and a draft exposure analysis methodology document. Comments from CASAC and the public were considered in a second draft AQCD, which was reviewed at a CASAC meeting held on November 18, 1999. After revision of the second draft AQCD, the final AQCD (US EPA, 2000) was released in August 2000. EPA put the review on hold when Congress called on the National Research Council (NRC) to conduct a review of the impact of meteorology and topography on ambient CO concentrations in high altitude and extreme cold regions of the U.S. In response, the NRC convened the committee on Carbon Monoxide Episodes in Meteorological and Topographical Problem Areas, which focused on Fairbanks, Alaska as a case study in an interim report, which was completed in 2002. A final report, "Managing Carbon Monoxide Pollution in Meteorological and Topographical Problem Areas," was published in 2003 (NRC, 2003) and offered a wide range of recommendations on management of CO air pollution, cold start emissions standards, oxygenated fuels, and CO monitoring. EPA did not complete the review which started in 1997.

1.4 SCOPE OF THE REVIEW

For the current review of the primary CO standard, relevant scientific information on human exposures and health effects associated with exposure to ambient CO will be assessed. The possible influence of other atmospheric pollutants on the interpretation of the role of CO in health effects studies will be considered. This will include other pollutants with the potential to co-occur in the environment (e.g., NO_2, SO_2, O_3, and PM). The review will also assess any

relevant scientific information associated with known or anticipated public welfare effects that may be identified.

2. REVIEW SCHEDULE

In September 2007, EPA's National Center for Environmental Assessment in Research Triangle Park, NC (NCEA-RTP) announced the initiation of the current periodic review of the air quality criteria for CO and the CO NAAQS and issued a call for information in the Federal Register (72 FR 52369). Table 2-1 outlines the schedule under which the Agency is currently conducting this review.[6]

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 (IRP)	March 2008
	CASAC consultation on IRP	April 2008
	Final CO NAAQS IRP	August 2008
Science Assessment	Prepare first draft of ISA	February 2009
	CASAC/public review first draft ISA	April 2009
	Prepare second draft of ISA	August 2009
	CASAC/public review second draft ISA	October 2009
	Prepare final ISA	January 29, 2010
Risk/Exposure Assessment	Prepare assessment methodology	March 2009
	CASAC/public consultation on methodology	April 2009
	Prepare first draft risk and/or exposure assessments	September 2009
	CASAC/public review of the first draft	October 2009
	Prepare second draft of risk and/or exposure assessments	February 2010
	CASAC/public review of second draft risk and/or exposure assessments	March 2010
	Prepare final risk and/or exposure assessments	May 28, 2010
Policy Assessment/ Rulemaking	Proposed rulemaking	October 28, 2010
	Final rulemaking	May 13, 2011

[6] This schedule is based on a court-ordered schedule that governs the completion of the review, *See Communities for a Better Environment v, EPA*, No. 07-3678 (N.D. Cal., May 5, 2008). Further orders of the court may require revisions to this schedule.

3. KEY POLICY-RELEVANT ISSUES

The key policy-relevant issues to be addressed in this review are presented below as a series of policy-relevant questions that will frame our approach to determining whether the current primary NAAQS for CO should be retained or revised and whether to set separate secondary standards. The ISA, health risk/exposure assessment, and any welfare-related assessment(s) to be conducted in this review will provide the basis for addressing these questions. The answers to these questions, and the resulting conclusions regarding the corresponding policy-relevant issues, will inform the policy assessment/rulemaking that will lead to the decision of whether to retain or revise the current 1-hour and 8-hour primary standards and whether separate secondary standards for CO are needed.

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. The secondary NAAQS for CO were revoked in 1985, and there currently are no secondary standards for CO. There was insufficient evidence of welfare effects occurring at or near ambient levels to justify setting secondary NAAQS in 1994. That review resulted in EPA's conclusion that the then existing primary CO NAAQS provided 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.

3.1 ISSUES TO BE CONSIDERED IN THE CURRENT REVIEW OF THE PRIMARY NAAQS

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) primary NAAQS for CO.

The first step in reviewing the adequacy of the current primary NAAQS 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. The ISA will consider 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 human subpopulations that are particularly sensitive to CO exposures? The NRC committee report (NRC, 2003) recommended additional research on effects of CO on birth outcomes. 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., neonates)?
- What do recent studies focused on the near-roadway environment, including bus stops and intersections, tell us about high-exposure human subpopulations and the health effects of CO? What information is available on elevated exposures due to other transportation sources, such as shipping, port operations, and recreational vehicles? What is the effect of altitude on CO sources and health effects?
- 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 (e.g.,tissue oxygenation) should be evaluated to characterize the biological effect?
- 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 standards 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, and conversely, is there evidence that suggests that effects occur only at higher levels than previously reported? 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?
- What range of levels is supported by the health effects evidence and air quality/exposure assessments, and what are the uncertainties and limitations in the health effects evidence and air quality/exposure assessments?
- What is the range of forms supported by the health effects evidence and air quality/exposure assessments, and what are the uncertainties and limitations in that health effects evidence and air quality/exposure assessments?

3.2 ISSUES TO BE CONSIDERED IN THE CURRENT REVIEW OF A POSSIBLE SECONDARY NAAQS

In this review, a series of policy-relevant questions will frame our approach to determining whether secondary NAAQS for CO should be considered. The answers to these questions, and the resulting conclusions regarding the corresponding policy issues, will inform the decision of whether to set secondary NAAQS for CO.

The first step in reviewing the possible need for secondary NAAQS is to consider whether the available body of scientific literature, assessed in the ISA, provides evidence of welfare effects related to exposure to CO in the ambient air. The ISA will evaluate the newly available scientific evidence and will address a series of questions including the following:

- Have new information or scientific insights altered the scientific conclusions regarding the occurrence of direct (or indirect) welfare effects associated with levels of CO found in the ambient air?
- At what levels of ambient CO do welfare effects of concern occur?
- To what extent is key scientific evidence becoming available to improve our understanding of the welfare effects associated with various time periods of CO exposures, including not only daily, but also chronic (months to years) exposures?
- Has new information, analytical tools/methods, or scientific insight altered conclusions from previous reviews regarding the plausibility of adverse welfare effects caused by CO exposure?
- To what extent have important uncertainties identified in the last review been reduced or new uncertainties emerged?

If the evidence suggests that setting a secondary standard or standards might be appropriate, we will consider whether the available body of evidence supports consideration of various options. The following questions will inform this determination:

- Is there evidence for the occurrence of adverse welfare 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 welfare effects will occur? If so, are these exposures of sufficient magnitude such that the welfare effects might reasonably be judged to be important from a public welfare perspective? What are the important uncertainties associated with these exposure estimates?
- Do welfare effects evidence and air quality/exposure assessments provide support for considering different exposure indices or averaging times?
- What range of levels is supported by the welfare effects evidence and air quality/exposure assessments, and what are the uncertainties and limitations in the welfare effects evidence and air quality/exposure assessments?
- What is the range of forms supported by the welfare effects evidence and air quality/exposure assessments, and what are the uncertainties and limitations in the welfare effects evidence and air quality/exposure assessments?

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, health effects, and welfare 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 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 final 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, including issues addressed in the NRC committee report on CO (NRC, 2003). 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 human clinical studies do not necessarily reflect effects in the most sensitive population, studies at higher exposure levels will be included when they provide information relevant to previously unreported effects, evidence of the potential mechanism for an observed effect, or information on exposure-response relationships.

4.2 ASSESSMENT APPROACH

Introduction

The EPA's National Center for Environmental Assessment in Research Triangle Park (NCEA-RTP) is responsible for preparing the ISA and the related annexes for CO. Expert authors include EPA staff with extensive knowledge in their respective fields and extramural scientists contracted to the EPA. A diagram showing the standard protocol for development of an ISA, including both health and ecosystem effects, is presented in Figure 4.1. While no secondary standard currently exists for CO, any evidence of welfare effects of ambient CO (such as effects on domestic and wild animals, crops and forest vegetation, and microorganisms) identified during ISA development will also be included. The ISA for CO will focus primarily on scientific evidence relating to health effects. A complete description of the new NAAQS review process is presented in Section 1.1.

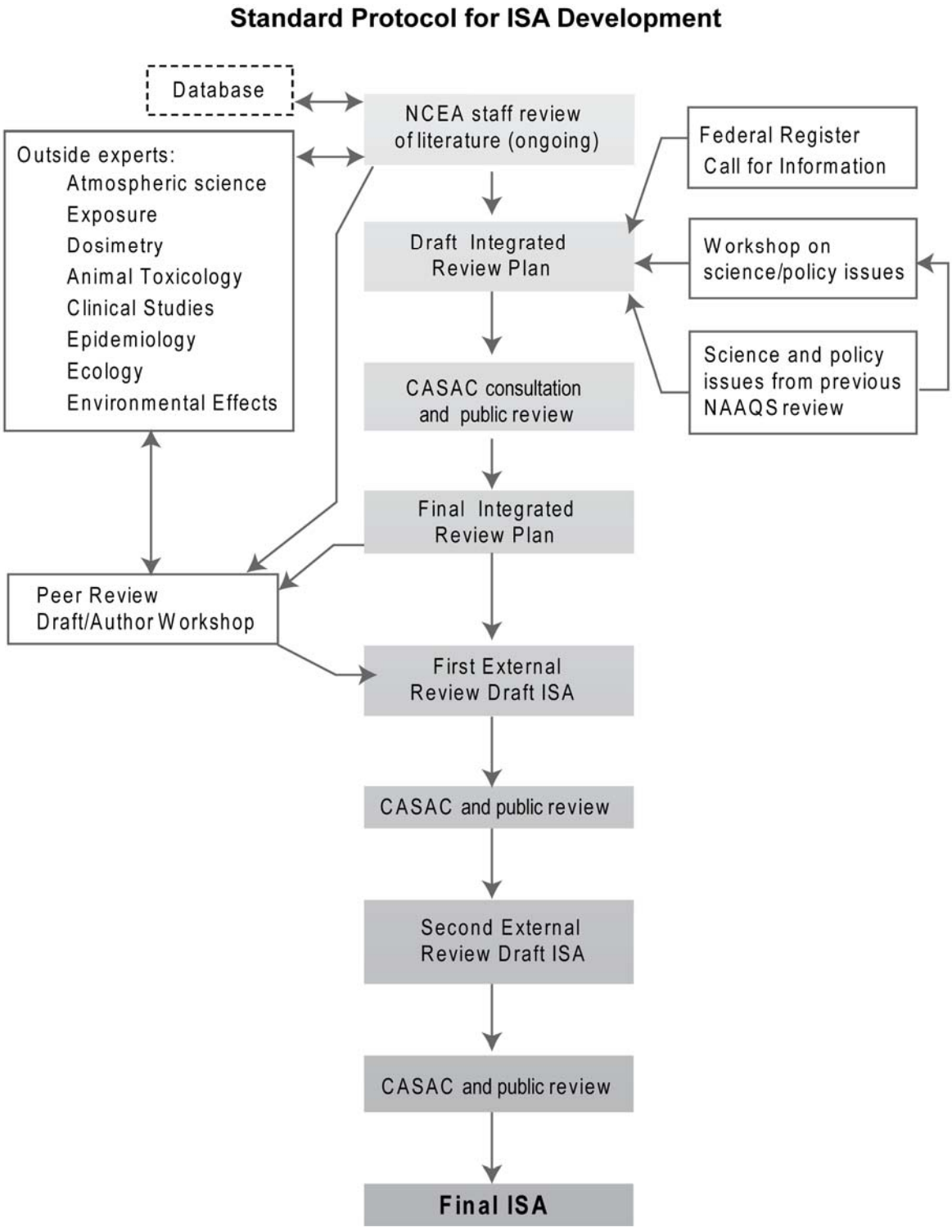

Figure 4.1. Protocol for ISA development, showing the steps involved in production of Integrated Science Assessments.

Literature Search

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, ISI Web of Knowledge, 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, ecological, 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 potentially 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 of population exposure 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, reliable comparisons between study groups?
- Are the health endpoint measurements meaningful, reliable, and clinically significant?

- Does the study contain unique data, such as the documentation of a previously unreported effect, documentation of the mechanism for an observed effect, or information on exposure-response relationships?
- Are the statistical analyses appropriate, properly performed, and properly interpreted with sufficient statistical power?
- Are likely covariates (i.e., potential confounders or effect modifiers) adequately controlled or taken into account in the study design and statistical analysis?
- Are the reported findings internally consistent, biologically plausible, and coherent in terms of consistency with other known facts?

Consideration of these issues, more fully discussed in Annexes, informs our judgments on the relative quality of individual studies and allows us to focus the assessment on the most pertinent studies.

Criteria for Selecting Epidemiological and Field Studies

In selecting epidemiological studies for the present assessment, EPA will consider whether a given study contains information on: (1) associations with measured CO concentrations using short- or long-term exposures at or near ambient levels of CO; (2) health effects of CO or indicators related to CO sources (e.g., motor vehicle emissions, fossil fuel combustion); (3) health endpoints and populations not previously extensively researched; (4) multiple pollutant analyses and other approaches to address issues related to potential confounding and modification of effects; and/or (5) important methodological issues (e.g., lag of effects, model specifications, thresholds, mortality displacement) related to CO exposure effects. All selected studies will be considered in the evaluation of the health evidence, including studies conducted in countries outside the United States and Canada. In drawing conclusions or recommendations pertinent for quantitative risk or exposure analyses, particular emphasis will be placed on those relevant to standard setting in the United States. Specifically, certain findings of studies conducted in the U.S. or Canada may be discussed in more detail than those from other geographic regions, as the potential impacts of housing characteristics, activity patterns, differing health care systems and the underlying health status of the populations need to be accounted for in the assessment. Emphasis in the text will be placed on discussion of (1) new, multi-city studies that employ standardized methodological analyses for evaluating CO effects and that

provide overall estimates for effects based on combined analyses of information pooled across multiple cities; (2) new studies that provide quantitative effect estimates for populations of interest; and (3) studies that consider CO as a component of a complex mixture of air pollutants.

Criteria for Selecting Human Laboratory, Clinical, and Animal Toxicological Studies

The review of research evaluating animal toxicological or controlled exposure studies will focus primarily on those studies conducted at physiologically relevant CO concentrations and those studies that approximate expected human exposure conditions in terms of concentration and duration. Studies that elucidate modes of action or mechanisms underlying biological effects and/or examine susceptibility will be considered.

The selection of research evaluating controlled human exposures to CO will focus on studies in which subjects were exposed at conditions relevant either to ambient exposures or to determination of mechanism. For these controlled human exposures, emphasis will be placed on studies that: (1) investigate potentially susceptible populations such as individuals with cardiovascular disease, particularly studies that compare responses in susceptible individuals with those in age-matched healthy controls; (2) address issues such as dose-response or time-course of responses; (3) investigate exposure to CO separately and in combination with other pollutants such as PM, O_3, NO_2 and SO_2; (4) are appropriately blinded and include control exposures to filtered air with subjects serving as their own controls; and (5) have sufficient statistical power to assess findings.

Review of the animal toxicological evidence will focus on studies that approximate expected human dose conditions, which will vary depending on the toxicokinetics and biological sensitivity of the particular laboratory animals examined. In addition, resource constraints prevent animal researchers from testing hypotheses that require large numbers of animals exposed to ambient levels of CO over a prolonged period. Consequently, animal studies are typically used to acquire data relating to mechanisms, and the exposures are purposefully high to assure a measurable response. Studies at high concentrations will be considered when they provide useful information to inform our understanding of interspecies differences and potential sensitivity differences between healthy and susceptible human populations.

Quality Assurance

Important quality assurance measures will be incorporated from the start of the current CO review. EPA uses an NCEA-RTP quality assurance plan for searching scientific literature which details an approach to gathering the scientific information found in peer-reviewed journal articles and government reports. Additionally, NCEA has data quality objectives which identify inputs to the science assessment and provide quality assurance (QA) instruction for researchers citing secondary information.

Content and Organization of the ISA

The organization of the ISA for CO will be consistent with that used in the recent draft ISAs for Oxides of Nitrogen and Oxides of Sulfur (US EPA, 2008, 2007). The ISA will contain information relevant to considering whether it is appropriate to retain or revise the current 1-hour and 8-hour standards and whether it is appropriate to consider setting a separate long-term exposure standard. The content of the ISA will be guided by a series of policy-relevant questions derived from the previous review of the CO NAAQS and from the Workshop to Discuss Policy-Relevant Science to Inform EPA's Integrated Plan for the Review of the Primary CO NAAQS, held on January 28-29, 2008 at the EPA campus in Research Triangle Park, NC. These policy-relevant questions are related to two overarching issues. The first issue is whether new evidence reinforces or calls into question the evidence presented and evaluated in the last NAAQS review. The second issue is whether uncertainties from the last review have been addressed and/or whether new uncertainties have emerged. The specific questions that stem from these issues are listed below by topic area.

Source to Dose

Air Quality and Atmospheric Chemistry: The ISA will present and evaluate data related to ambient concentrations of CO; sources leading to the presence of CO in the atmosphere; and chemical reactions that determine the formation, degradation, and lifetime of CO in the atmosphere.

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

- Using recent air quality and emissions data, what are the current emission levels and ambient concentrations of CO in the US? What spatial and temporal patterns can be seen in these CO air quality data, and how do these relate to patterns of human exposure? What are the effects of sample and measurement averaging time and range on the level of spatial and temporal variability in concentrations? To what extent are ambient CO concentrations correlated with other air pollutants (e.g., NO_x, O_3, PM, SO_x), and do these possible correlations change spatially and temporally in significant ways? On what spatio-temporal scales does CO affect the production of ozone and other related pollutants?
- The NRC committee report (NRC, 2003) identified the spatial variability of CO concentrations and the likely existence of high-concentration hot spots, potentially near susceptible subpopulations, as important issues in assessing the CO regulatory monitoring network. What are the implications of the current network configuration for the interpretation of CO-related health effects?
- Using air quality and emissions data on CO and atmospheric chemistry models, what are likely policy relevant background concentrations of CO?
- Are there other techniques that can be used to better define the range of concentrations and the spatial and temporal variability of CO over the U.S.? Are satellite retrievals or three dimensional chemical transport models useful? Can satellite data be used on a regular basis to improve the characterization of CO emissions?
- What information is available on short-term ambient CO concentrations (< 1 hr)?

Human Exposure: The ISA will evaluate the factors that influence exposure to CO and the uncertainties associated with extrapolation from ambient concentrations to personal exposures to CO of ambient origin, particularly in the context of interpreting results from epidemiologic studies. The issues of uncertainty differ by the exposure period of interest. Short-term exposure studies (e.g., population-level studies using time-series analyses, field/panel studies) primarily rely on temporal variation in exposure, while long-term exposure studies (e.g., longitudinal cohort studies) rely on spatial variability of exposure.

- What data exist on relationships between exposure to CO and corresponding exposure to gaseous and particulate co-pollutants (e.g., NO_x, O_3, PM, SO_x)? What factors affect these relationships (season, housing characteristics, activity patterns, etc.)?
- What are the uncertainties when extrapolating between stationary CO monitoring instruments and personal exposure to CO of ambient origin, especially for susceptible groups? Issues include measurement error in outdoor ambient monitors, the use of monitors for estimating community concentrations, and their use as a surrogate for personal exposure to CO of ambient origin.
- What information is available on exposures to short-term (< 1 hr) peak CO concentrations?
- To what extent do measurements from ambient CO monitors provide an estimate of ambient exposures for health studies, serve as an indicator of personal exposure to CO, and/or serve as an indicator of personal exposure to other gaseous pollutants (including O_3 and NO_2) and particulate pollutants generated by traffic?
- What influence do the temporal and spatial patterns of CO exposure, for both indoor and outdoor sources, have on evaluation of health effects? What is the exposure pattern for indoor sources, such as gas stoves and space heaters (i.e., peak, repeated peak, and average CO) and how does it relate to ambient CO patterns?
- What evidence is available on subpopulations likely to have high ambient CO exposures including those living, working and/or attending school near roadways and those in the vicinity of shipping or port operations?
- What data are available to interpret both short- and long-term CO exposures (e.g., <1 hour, 1 hour, 8 hours, 24 hours, 2 weeks, or longer)? What data and models are available to support exposure estimates over periods that may be relevant to additional health endpoints, such as birth outcomes? This includes such information as air exchange rates, indoor sources, distance to highways, and performance indicators for methods of measuring personal exposures to CO (particularly at low ambient levels).
- How do modeled predictions of CO concentrations and exposures compare with monitoring results?

Dosimetry of Inhaled CO: The ISA will evaluate the literature relating to pharmacokinetic modeling of CO uptake and the associated formation of COHb. Recent information relating to either the well-established Coburn-Forster-Kane model or alternative models will be integrated with literature summarized in the previous AQCD to assess the current state of knowledge on COHb formation. The ISA will assess evidence on uncertainties in modeling COHb as a function of inhaled CO. The contribution of endogenously produced CO to COHb is included in the Coburn-Forster-Kane model and will be considered in the integrative health effects section of the ISA.

- What new information is available on the validity and applicability of the Coburn-Forster-Kane model? Are alternative approaches available and preferable for modeling COHb formation from ambient CO?
- What factors contribute to uncertainty and variability in estimating COHb formation from ambient CO?
- What information is available on COHb formation in fetuses and infants? Issues to be considered include COHb pharmacokinetics in neonates and the relationship between maternal CO exposure and fetal COHb concentration.

Health Effects

The ISA will evaluate the literature related to health effects identified in the 2000 AQCD, as well as any additional health outcomes identified during the review. Previously identified health effects include cardiovascular effects (e.g., myocardial ischemia, angina, arrhythmia), central nervous system effects (e.g., loss of dexterity, visual impairment), respiratory effects, and birth outcomes (e.g., low birth weight, preterm birth) associated with short and/or long term exposure to CO. This will include evaluation of emergency department visits, hospitalizations, and mortality associated with these effects. Health effects that are associated with both short- and long-term exposures will be evaluated in epidemiologic, human clinical, and toxicologic studies. Recent studies regarding the formation of endogenous CO by cells and tissues and the resulting localized biological response will be evaluated in order to determine the relevance to

biological responses following ambient CO exposure. Causality, uncertainty, biological mechanism of action, susceptible and vulnerable populations, and public health impact will all be considered. The data will be reviewed with the understanding that effects from ambient CO must be considered in conjunction with co-occurring pollutants (e.g., NO_x, O_3, PM, SO_x).

For a given type of health outcome, the ISA will evaluate the strength, robustness and consistency of the findings from the different disciplines. The health findings will be further integrated, using the toxicologic and human clinical studies to assess biologic plausibility and mechanistic evidence for the epidemiology findings. A key focus of the integration of health evidence will be on the attribution of health effects to CO as a component of multipollutant exposures. Efforts will be directed at identifying the lower levels at which effects are observed and at determining concentration-response relationships for CO. Concentration-response relationships among these studies will be evaluated for coherence. The ISA will evaluate the scientific evidence on the occurrence of health effects from long-term or short-term exposure to CO at ambient levels. The ISA will also assess the evidence for uncertainties related to these associations and information on the public health implications related to ambient CO exposure. The evaluation will also focus on which exposure durations and developmental time periods of exposure are most strongly associated with effects, for both short-term and long-term exposures.

Short-Term Exposure:

- 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 in both healthy individuals and in those with preexisting disease states (e.g., individuals with cardiovascular or ischemic heart disease)? What new evidence is available on effects occurring from exposures at sub-daily averaging times?
- What are the effects of CO exposure on breathing rate and respiratory gas exchange in healthy and susceptible individuals (e.g., oxygen diffusion capacity and ventilation-perfusion mismatches) and what is the potential clinical relevance of these effects? Does recent evidence indicate other respiratory effects from ambient CO exposure?

- 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? Do other gaseous pollutants and/or particulate matter confound or modify the effect observed due to exposure to CO? 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 developmental effects of CO exposure?
- 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?
- What biomarkers of early effect may be used in the assessments? What detectable biological changes will be considered adverse health effects?

Long-Term Exposure:

- Does the scientific evidence support the occurrence of health effects from long-term exposure (e.g., months to years) at ambient levels that are lower than previously

observed? If so, what uncertainties are related to these associations, and are the health effects in question important from a public health perspective?

- Can long-term exposures to CO result in chronic effects such as developmental effects or birth outcome effects?
- What are relevant exposure periods for effects associated with birth outcomes? What metrics are appropriate for assessing developmental effects (e.g., low birth weight, preterm birth)? Are certain effects linked to specific exposure windows?
- To what extent does long-term CO exposure promote development of chronic cardiovascular disease? What is the relationship between long-term CO exposure and shortening of human life span via promotion of such diseases?
- Are there annual and seasonal patterns of CO exposure that are associated with potentially harmful health effects?

Causality: The ISA will evaluate the evidence relating to the existence or lack of a causal relationship between observed health outcomes and CO exposure using a framework developed by NCEA for the recent NO_X ISA (U.S. EPA, 2008). This framework is designed to improve consistency and transparency by establishing uniform language to describe causal relationships and explicitly outlining the guidelines that are used to evaluate causality. These guidelines are based on those proposed by Sir Austin Bradford Hill in 1965 (Hill, 1965), including: consistency, strength, specificity, and temporality of the observed association; evidence of an exposure-response relationship; biological plausibility and coherence; experimental evidence from human populations; and analogy (e.g. mode of action for structural analogs). Individual studies may not provide information on all of these factors, yet remain informative for inferring causality. This approach draws from and is consistent with similar approaches formulated by government agencies and the wider scientific community, including the Institute of Medicine (IOM, 2007), the International Agency for Research on Cancer (IARC, 2006), the National Toxicology Program (NTP, 2005), EPA (U.S. EPA, 2005), and the Centers for Disease Control and Prevention (CDC, 2004). Biological plausibility and coherence of the evidence will be key considerations in drawing conclusions about causality. The ISA will place emphasis on studies

conducted at or near typical ambient levels, except regarding evidence of biological plausibility and mechanisms, as these may only be observable in animal or human exposure study populations at higher levels than they might be observed in susceptible human populations. The ISA will also assess any information available from "intervention" studies regarding the health impacts of decreases in ambient levels of CO that is relevant to the evaluation of causality in CO-health outcome relationships or benefits accruing from such interventions.

- Does the evidence base contain new information to evaluate the case for or against a causal relationship between health effects and CO exposure?
- What information is available regarding the health impacts of a decrease in ambient levels of CO?
- What insights can be gained regarding causality by comparing health effects observed in older multipollutant studies (with comparatively higher ambient CO levels) with more recent multipollutant studies?

Uncertainties: The ISA will evaluate uncertainty in the scientific data, particularly in relation to observed epidemiologic findings and their consistency with human laboratory, clinical, and animal toxicologic studies in terms of observed effects and biological pathways.

- How does confounding by coexposure to other pollutants (e.g., O_3, PM, SO_2, and NO_2) and meteorological factors influence the associations observed with CO for both short- and long-term exposures? The manner in which ambient CO concentration may serve as a surrogate for exposure to vehicle exhaust pollutants, including gases and particles, will be discussed.
- What are the uncertainties due to other factors in epidemiologic studies (e.g., demographic and lifestyle attributes, genetic susceptibility factors, occupational exposure, and medical care)?
- What is the shape of the concentration-response function (e.g., linear vs. threshold models)?
- What are the uncertainties associated with comparing the results of birth outcome studies utilizing different study designs, metrics, and endpoints?

- What uncertainties surround the evidence for long-term effects such as life shortening and development/progression of disease?

Biological Mechanisms of Action: The ISA will evaluate the data examining mechanisms for 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., tissue oxygenation)?
- What are the effects of age, gender, and pre-existing disease on cellular and tissue responses and the pathophysiology of CO-induced injury?
- What physiological characteristics of 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., persons with cardiovascular disease, COPD, or reduced or abnormal hemoglobin, older adults,

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 individuals who are healthy 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 mechanisms through which CO may be acting for these groups? Do pathophysiologic changes in these populations alter the normal compensatory responses to CO exposure observed in healthy individuals? What is the nature and time-course of the development of effects in healthy persons and in persons with preexisting disease?
- Is preexisting respiratory or cardiovascular disease in conjunction with advanced age an important factor in susceptibility to mortality associated with exposure to CO?
- Regarding morbidity health endpoints, to what extent are older adults and neonates more sensitive than the general population to CO exposure?
- How should sensitive subpopulations be considered in interpretation of epidemiological results and exposure-response characteristics, considering that these results may be driven by the more sensitive subpopulations?
- Is susceptibility to the effects of short-term CO exposure associated with long-term CO susceptibility?
- What host and environmental factors (e.g., demographic, socioeconomic, and genetic) are associated with susceptibility to short- and long-term exposure to CO?

Public Health Impact: The ISA will present concepts related to the potential for defining adverse health effects. To accomplish this, the implications for public health of different health effects will be discussed. This will include, as appropriate, an estimation of the potential number of persons at risk in specific susceptible and vulnerable at-risk population groups. The concept of attributable risk, which considers the exposure of a subpopulation along with relative risk, will

be evaluated in consideration of the public health impact. Low-level effects will be interpreted in light of the policy-relevant background concentration of CO. Furthermore, the analysis will identify and address, as appropriate, disproportionately high and adverse human health or environmental effects of CO on minority populations and low-income populations, as recommended in the NRC committee report (NRC 2003).

Annexes to the ISA

The ISA will be supplemented by a series of annexes, which will provide detailed supporting information and more comprehensive coverage of research areas summarized in the ISA. While studies with the most policy-relevant information are summarized in the ISA, the annexes present information on all studies considered during the review. Annexes also provide in-depth discussion of scientific topics supporting interpretation of exposure, health, and welfare effects. The annexes will provide information on: (1) the chemistry, physics, sources, and emissions of CO, as well as sampling and analytic methods for measurement of CO; 2) environmental concentrations and human exposure to CO; (3) dosimetry; (4) toxicologic studies of CO health effects in laboratory animals and in vitro systems; (5) human clinical studies examining health effects following controlled exposure to CO; and (6) epidemiologic studies of health effects from short- and long-term exposure to CO. More detailed information on various methods and results for the health studies will be summarized in tabular form in the annexes. These tables will generally be organized to include information about: (1) concentrations of CO levels and averaging times; (2) description of study methods employed; (3) results and comments; and (4) quantitative outcomes for CO measures. Additionally, annexes will contain background material on legislative requirements, the NAAQS review process, and the history of earlier CO reviews.

4.3 SCIENTIFIC AND PUBLIC REVIEW

Drafts of the ISA will be reviewed by the CASAC CO Review Panel of EPA's Science Advisory Board (SAB) and made available for public comment. The annexes to the ISA will also be made available to CASAC in order to assist with their review; however, CASAC members will not be specifically charged with reviewing the annexes. The CASAC CO Review

Panel will review the first draft ISA and discuss their comments in a public meeting announced in the Federal Register. Based on CASAC's past practice, EPA expects that the CASAC chair will summarize key CASAC advice and recommendations for revision of the document in a letter to the EPA Administrator. In revising the first draft ISA for CO, EPA will take into account any such recommendations, as well as comments received from CASAC or from the public at the meeting itself and any written comments received. EPA will prepare a second draft ISA for CASAC review and public comment. The CASAC CO Review Panel will review the second draft ISA and discuss their comments in a public meeting announced in the Federal Register. Again, based on CASAC's past practice, EPA anticipates the CASAC chair will summarize key advice and recommendations for revision of the second draft ISA in a letter to the EPA Administrator. In finalizing the ISA, EPA will take into account any such recommendations. EPA will also consider comments received from CASAC or from the public at the meeting itself and any written public comments. After appropriate revision, the final document will be made publicly available on an EPA website and in hard copy. A notice announcing the availability of the final ISA will be published in the Federal Register. In addition, the final ISA will be placed in the rulemaking docket.

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 draft 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 exposure assessment and risk characterization 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 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 draft Health Assessment Plan: Scope and Methods for Exposure and Risk Assessment (hereafter, "Health Assessment Plan"). The Health Assessment 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 first draft risk and exposure assessment (REA) document will be prepared based on the draft Health Assessment Plan and will assess exposure and characterize health risks associated with recent air quality and air quality just meeting the current CO NAAQS. The second draft REA document will reflect comments from the CASAC CO Panel and the public and will also analyze exposure and characterize health risks associated with any potential alternative CO standards under consideration. The REA document will be made final upon completion of the final ISA for CO and following review of the second draft REA document by the CASAC CO 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 basis for assessing protection afforded by the current CO standards and preliminary insight into the relative impact of certain indoor sources to total CO exposure. Denver was chosen because (1) in 1988 it violated both the current 1-hour and 8-hour CO NAAQS (one of only two areas that exceeded both standards at the time); (2) it had a relatively high 8-hour design value, 16.2 ppm -- the second-highest design value in the U.S. at the time; and (3) CO personal monitoring data were available for a rough validity check of the modeling effort. Four scenarios were modeled that provided insight into exposures related to (1) current air quality versus future air quality associated with just meeting the 8-hour CO NAAQS and (2) common indoor sources present versus ambient air without these indoor sources. Only the 8-hour NAAQS was evaluated since previous analyses indicated that it was the controlling standard for attainment (US EPA, 1979b). Indoor sources that were considered included residential gas stoves and passive smoking. Other indoor sources, such as running automobiles in private or public garages and CO intrusion into a motor vehicle from the vehicle itself, were not included in any of the scenarios.

The model used for exposure analysis was pNEM/CO (probabilistic NEM applied to CO*)*, a version of the CO NAAQS Exposure Model (NEM) that incorporated Monte Carlo sampling and multiple runs, or realizations, of the model. The major model outputs of interest were estimates of the number of person-days of exposure to various CO levels for the four scenarios mentioned above for adults with cardiovascular disease in Denver. In addition, estimates also were made of the percentage of the cardiovascular heart disease population in Denver that would exceed selected COHb levels one or more times per year under the four scenarios. The estimates of COHb were derived by applying a modified version of the Coburn-Forster-Kane (CFK) differential equation that estimates COHb levels from CO exposure as a function of time and physiological and environmental factors (e.g., blood volume, altitude,

endogenous CO production rate). It was estimated at the time that there were about 36,800 non-smoking adults in Denver with diagnosed or undiagnosed (silent) ischemia.

The analysis indicated that if the current 8-hour standard were just met, the proportion of the nonsmoking population with cardiovascular disease experiencing exposures at or above 9 ppm for 8 hours decreased by an order of magnitude or more, down to less than 1 percent of the total person-days in that population. Likewise, meeting the current 8-hour standard reduced the proportion of the nonsmoking cardiovascular-disease population person days at or above COHb levels of concern by an order of magnitude or more. Upon meeting the 8-hour standard, EPA estimated that less than 0.1 percent of the nonsmoking cardiovascular-disease population would experience a COHb level of about 2.1 percent. A smaller population was estimated to exceed higher COHb percentages. Based on this assessment, and considering the 1985 review of similar CO effects and effects levels, the Administrator concluded that the evaluation of adequacy of the existing CO standards should focus on reducing the number of individuals with cardiovascular disease from being exposed to CO levels in the ambient air that would result in COHb levels of 2.1 percent or greater. The Administrator concluded that standards that limit the occurrence of COHb levels above 2.1 percent would provide an adequate margin of safety against effects of uncertain occurrence in the range of 2.1 to 2.9 percent, as well as those of clear concern that have been associated with COHb levels in the range 2.9 to 5.9 percent. The Administrator also concluded that relatively few people of the cardiovascular sensitive population group analyzed would experience COHb levels $\geq$ 2.1 percent when exposed to CO levels in the absence of indoor sources when the current ambient standards are attained. The analysis also indicated, however, that certain indoor sources (e.g., passive smoking, gas stove usage) contributed to total CO exposure but could not be effectively mitigated by ambient air quality standards.

The 8-hour standard was chosen because most individuals, even at rest, appeared to approach equilibrium levels of COHb after 8 hours of exposure. In addition the 8-hour period approximated blocks of time for which people are often exposed in a particular location or activity (e.g., sleeping, working) and provided a good indicator for tracking continuous exposures that occurred during any 24-hour period. The 1-hour standard was chosen because a 1-hour averaging period provided a better indicator of short-term health effects of CO and a l-hour standard provided reasonable protection from effects that might be encountered from very short duration peak exposures in the urban environment. Review of scientific information in the

1991 Criteria Document indicated that these reasons for choosing averaging times for the CO standards remained valid and there were no compelling arguments for selecting new or different averaging times. The Administrator also considered and concurred with the staff recommendations contained in the 1992 Staff Paper that both averaging times should be retained for the primary CO standards. For the above reasons, the Administrator determined under section 109(d)(1) that revisions of the 1-hour (35 ppm) and 8-hour (9 ppm) primary standards for CO were not appropriate at that time.

1999 Exposure Analysis for Denver

Additional exposure analyses were planned in 1999 using the Denver and Los Angeles (LA) areas to provide estimates of CO exposures and resultant COHb levels for adults in two urban areas. Denver was included in the planned analyses for comparison purposes because it was the only city included in the exposure analysis conducted in the previous review. In addition, Denver was one of a few areas where a personal CO exposure study had been conducted. After an initial review of the methodology, EPA planned to also conduct the analyses for LA for several reasons: (1) it presented the largest potential public health burden due to its ambient CO levels and potential population exposure; (2) an extensive monitoring network was available; and (3) an existing study of personal and indoor CO concentrations that potentially could be used to evaluate the model had been conducted in Los Angeles. The primary target population was adults with cardiovascular disease, as it was in the 1992 analysis. The 1999 analysis initially focused on several scenarios: (1) current air quality (1995 for Denver); and (2) the presence of indoor sources (gas stoves/ovens and passive smoking) versus ambient air without indoor sources. The analyses were intended to provide a basis for assessing protection afforded by the current CO standards and preliminary insight into the relative impact indoor sources may have on total exposure. The model selected to estimate population exposure was an updated version of pNEM/CO that was used in the 1992 Denver analysis, with the major outputs of interest being estimates of the number and percentage of person-days of exposure to various CO levels and the number and percentage of person-hours and people exceeding various COHb levels. Only the 8-hour NAAQS was planned for evaluation because previous analyses indicated that it was the controlling standard for attainment.

A draft exposure analysis report (Johnson et al, 1999) applying the updated exposure model only to the Denver area was provided to the CASAC CO Panel and made available for public review in March 1999 for the purpose of obtaining scientific and public input on the proposed methodology. The CASAC CO Panel conducted a consultation on the methodology for the analysis on June 9-10, 1999. The CO NAAQS review was put on hold, however, and the exposure analysis was not completed. For this current review, EPA staff will build upon the 1999 work and subsequent improvements to the exposure model in developing its plan for CO exposure assessment.

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) and information contained within the draft 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 the exposure/risk assessment will be to conduct an air quality analysis relying 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, and policy-relevant background levels[7]. 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.

7 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.

- 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
- Estimate number of exceedances of several short-term peak air quality indicators given attainment of the current CO standards and potential alternative standards.
- Develop methods to adjust recent CO air quality data to simulate just meeting the current standards and any alternative CO standards. EPA will consider alternative air quality simulation procedures, including a proportional rollback procedure, for use in this current review. EPA will also evaluate candidate procedures for simulating changes in CO air quality likely to result from just meeting the current or alternative standards based on analyzing changes in CO levels that have been observed historically and/or analyzing changes in CO levels predicted by air quality models. EPA will consider factors which may influence the concentration distributions such as potential source contributions, as well as the influence of local and regional pollution.
- Evaluate the relationship between 1-hour and 8-hour peak concentrations across multiple years for different geographic areas.

Exposure Assessment

The general approach would be to estimate population exposures to ambient CO in one or more urban areas across the United States. Areas included in the analysis would be selected with the goal of achieving variation in population, geography, demographics, climate, and CO air quality. Exposure estimates would be generated for current CO levels, for levels adjusted to just meet the current NAAQS, and for levels adjusted to simulate just meeting potential alternative standards.

The exposure assessment would take into account several important factors including the magnitude and duration of exposures, frequency of repeated high exposures, and breathing rate of individuals at the time of exposure. Estimates would be developed for multiple indicators of exposure including (1) counts of people exposed one or more times to a given CO concentration while at a specified breathing rate and (2) counts of person-occurrences of particular exposures, which accumulate across all people in the population of interest.

EPA's Air Pollutants Exposure (APEX) model (also referred to as the Total Risk Integrated Methodology/Exposure (TRIM.Expo) model) would be used in this analysis. APEX is a Monte Carlo simulation model that can be used to simulate a large number of randomly sampled individuals within each area thus generating area-wide estimates of population exposure. APEX simulates exposures in indoor, outdoor, and in-vehicle microenvironments while taking into consideration the movement of individuals through time and space. A user's guide and technical support document describe the APEX model in detail (U.S. EPA 2006 a,b). The choice of areas to model and the exposure assessment methodology will be described in detail in the draft Health Assessment Plan.

5.4 RISK CHARACTERIZATION APPROACH

A two-tiered approach to characterizing health risks will be employed. In a first tier analysis, potential health effect benchmarks will be identified based on information in the draft ISA. These health benchmark levels would be combined with exposure or dose estimates from the exposure/dose assessment in order to characterize population health risks. In a second tier risk analysis, which would be conducted only if judged appropriate and if relevant data are available, an assessment using concentration-response or exposure/dose-response data would be conducted by combining this data with either ambient distributions or estimated exposure or dose distributions, respectively.

The goals of a CO risk characterization would be: (1) to estimate the number of people exposed to CO concentrations or COHb levels above health effects benchmarks considering current air quality and air quality levels simulated to just meet the current and potential alternative CO standards; (2) to provide distributions of health risk estimates associated with recent air quality and air quality just meeting the current and potential alternative standards if a second tier risk analysis is conducted; and (3) to identify key assumptions and uncertainties in the risk estimates.

Health Effect Benchmarks

This type of risk characterization would use exposure and/or dose (e.g., COHb) estimates, along with potential health effect benchmarks that may be identified based on information in the draft ISA and relevant Annexes, to estimate (1) the number of individuals with exposures above

levels expected to cause adverse health effects, and (2) the percent of at risk populations experiencing exposures and/or dose levels of concern. Multiple exposure scenarios will be considered, including exposure associated with current ambient air quality, with current air quality levels enhanced by including local source contributions, and/or with levels of CO associated with simulating just meeting the current and potential alternative standards. The potential health effect benchmarks will account for those individuals who are particularly susceptible and/or vulnerable to the effects of CO (e.g., cardiopulmonary disease populations). The health risk characterization would require that averaging times be comparable for any estimated exposure or dose concentrations and health metrics.

Dose-Response and Concentration-Response Functions

Incorporating dose-response or concentration-response data into the risk characterization will depend on the availability of data from controlled human exposure studies and epidemiologic studies, respectively. If quantitative relationships provided by studies or derived from the data presented in studies are available that describe the change in concentration (either ambient or exposure) or dose (e.g. COHb level) associated with a change in health response, then these relationships could potentially be applied to estimate health risk.

Controlled human exposure studies involve volunteer subjects who are exposed to specified levels of CO under controlled conditions for specified lengths of time. The endpoints of interest in previous reviews were related to the cardiovascular and central nervous systems, including decrement in time to onset of chest pain and ST-segment suppression in patients with angina pectoris, reduced maximal exercise duration in healthy adults due to decreased oxygen uptake, increased number and complexity of arrhythmia in individuals with chronic arrhythmia, and short-term effects on hand-eye coordination and vigilance in healthy individuals. In the prior reviews, these responses formed the basis for the development of health benchmarks related to specified COHb levels.

In contrast, epidemiological studies typically provide estimated concentration-response relationships based on data collected in environmentally-relevant settings. Ambient CO concentration is typically included in health effects models as the average of monitor-specific measurements. Common health responses that have been evaluated for CO include developmental effects, as well as cardiac and respiratory morbidity and mortality. In the

previous review the epidemiologic evidence was judged to be too limited to form the basis for developing either potential health benchmarks or quantitative risk estimates. Again, depending on the type of health response function(s) available, ambient CO concentration data might be used for characterizing risks, and are most appropriately applied in the geographic area where the epidemiological study was performed. It should be noted that a risk characterization based on epidemiological studies also requires baseline incidence rates and population data for the risk assessment locations.

Based on our current understanding of the available evidence, we do not anticipate that there will be sufficient exposure- or dose-response data from controlled human exposure studies to characterize health risks in this manner. However, there may be limited data available to develop concentration-response relationships from recently conducted epidemiologic studies. Following review of the draft ISA and considering comments and recommendations from CASAC and the public, the draft Health Assessment Plan will be designed to include such a proposed approach to characterizing health risk if warranted.

5.5 ASSESSMENT CRITERIA

Criteria will be established and described in the draft Health Assessment Plan to determine the level of detail warranted and the specific design of the assessments. The criteria will be designed to determine the value added to the assessment as measured by the reduction of uncertainties in the exposure and risk estimates. In order to determine which level of detail is warranted, the following factors will be considered by the workgroup and EPA management:

- Results of the ambient air quality indicator analysis;
- Weight-of-evidence, as provided in the ISA, from new controlled human exposure studies with relevant exposure-response data, particularly those conducted at or near current ambient concentrations;
- Weight-of-evidence, as provided in the ISA, from new epidemiological studies that evaluate the relationship between short-term repeated peak exposures and health outcomes;

- New information regarding susceptible populations identified in previous reviews (e.g., those with pre-existing cardiovascular disease) or information regarding newly identified susceptible populations;
- Information and data defining the potential impact of roadway CO concentrations on nearby residents and on specific microenvironmental concentrations (e.g., while traveling inside motor vehicles);
- Analysis of exposure studies using non-routine monitoring, other local sources (e.g., rail-yards, airports), and/or modeled CO concentrations;
- Existence of the data required to perform the analyses in each stage of the assessment.

5.6 UNCERTAINTY AND VARIABILITY

The uncertainty and variability inherent in estimates of exposure and risk will be characterized regardless of the type of exposure assessment and risk characterization conducted. Uncertainty reflects the degree of confidence in the representativeness of models or model components. Variability can be described in terms of empirical quantities that are inherently variable across time and space or between individuals (Cullen and Frey, 1999).

Assessing uncertainty and variability will begin with a qualitative analysis and progress to a quantitative analysis if data are available to support such an analysis. The first step in the uncertainty analysis will be to identify the components of the assessment, determine whether uncertainty can be evaluated for each of those components, and provide a rationale for why this is the case. The second step will be to perform a qualitative uncertainty analysis for the appropriate components of the assessment. This qualitative analysis will result in a matrix describing, for each area of uncertainty, both the magnitude (minimal, moderate, major) and the direction of influence (under- or over-estimate) on risk/exposure estimates. If sufficient data are available, and if the magnitude of uncertainty is judged significant, a quantitative assessment of uncertainty will then be performed for selected components of the assessment.

There are two primary sources of uncertainty that would be addressed in a quantitative analysis. The first is uncertainty associated with the model inputs (e.g., use of air quality data, time-location-activity diaries, microenvironmental factor distributions). The second is uncertainty associated with model formulation (e.g., algorithms included in the model).

5.7 PUBLIC AND SCIENTIFIC REVIEW

The CASAC CO Review Panel will be consulted on the assessment approach at a public meeting. Drafts of the REA document will also be reviewed by the CASAC CO Review Panel. The CASAC CO Review Panel will review the draft document and discuss their comments in a public meeting announced in the Federal Register. Based on CASAC's past practice, EPA expects that key advice and recommendations for revision of the document will be summarized by the CASAC Chair in a letter to the EPA Administrator. In revising the draft REA document for CO, EPA will take into account any such recommendations, and will also consider comments received, from CASAC or from the public, at the meeting itself and any written comments received. EPA anticipates preparing a second draft of the REA document for CASAC review and public comment. After appropriate revision, the final document will be made available on an EPA website, with its public availability being announced in the Federal Register.

6. POLICY ASSESSMENT/RULEMAKING

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.

Based on the information in the ISA and the exposure assessment report, EPA will publish a notice of proposed rulemaking to provide an opportunity for CASAC and the public to evaluate the policy options under consideration and to offer comments and recommendations to inform the Administrator's decision whether to retain or revise the primary CO NAAQS, and whether to promulgate a secondary NAAQS for CO.[8] Issuance of a final decision will complete the rulemaking process.

[8] As noted above in Chapter 1, EPA is also considering whether, and at what point in the process, to issue an ANPR.

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Postal information in this section where appropriate.