EPA

Carbon Monoxide National Ambient Air Quality Standards: Scope and Methods Plan for Health Risk and Exposure Assessment

April 2009

Office of Air Quality Planning and Standards
U.S. Environmental Protection Agency
Research Triangle Park, NC 27711

EPA-452/R-09-004
April 2009

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Office of Air and Radiation
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This Carbon Monoxide National Ambient Air Quality Standards: Scope and Methods Plan for Health Risk and Exposure Assessment (also referred to in this document as the Plan) has been prepared by the Office of Air Quality Planning and Standards, U.S. Environmental Protection Agency (EPA). Any opinions, findings, conclusions, or recommendations are those of the authors and do not necessarily reflect the views of EPA. This document is being circulated to facilitate consultation with the Clean Air Scientific Advisory Committee (CASAC) and for public comment. Comments on this document should be addressed to Dr. Ines Pagan (email: pagan.ines @epa.gov), U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards, C504-6, Research Triangle Park, North Carolina 27711.

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List of Acronyms/Abbreviations

APEX	EPA's Air Pollutants Exposure model
AQCD	Air Quality Criteria Document
AQS	EPA's Air Quality System
CAA	Clean Air Act
CASAC	Clean Air Scientific Advisory Committee
CFK	Coburn-Forster-Kane equation
CHAD	EPA's Consolidated Human Activity Database
CO	Carbon monoxide
COHb	Carboxyhemoglobin
CTPP	Census Transportation Planning Package
EPA	United States Environmental Protection Agency
GC	Gas chromatography
Hb	Hemoglobin
hr	Hour
ISA	Integrated Science Assessment
IRP	Integrated Review Plan
MET	Metabolic equivalents by activity
NAAQS	National ambient air quality standards
NCEA	National Center for Environmental Assessment
NEI	National Emissions Inventory
NEM	NAAQS Exposure Model
NCDC	National Climatic Data Center
NRC	National Research Council
NWS	National Weather Service
OAQPS	Office of Air Quality Planning and Standards
OAR	Office of Air and Radiation
ORD	Office of Research and Development
O2	Oxygen
pNEM	Probabilistic NAAQS Exposure Model
ppb	Parts per billion
ppm	Parts per million
PRB	Policy-relevant background
REA	Risk and Exposure Assessment
SD	Standard deviation
TRIM	EPA's Total Risk Integrated Methodology

1. INTRODUCTION

The U.S. Environmental Protection Agency (EPA) is presently conducting a review of the carbon monoxide (CO) national ambient air quality standards (NAAQS). EPA's overall plan and schedule for this CO NAAQS review are presented in the Plan for Review of the Carbon Monoxide National Ambient Air Quality Standards (US EPA, 2008b), or Integrated Review Plan (IRP). This IRP (US EPA, 2008b) outlines the Clean Air Act (CAA) requirements related to the establishment and periodic review of the NAAQS and the process and schedule for conducting the current CO NAAQS review. It presents the key policy-relevant issues to be addressed in this review 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. [1] The IRP also discusses two key components in the NAAQS review process – an Integrated Science Assessment (ISA) and a Risk and Exposure Assessment (REA) – in addition to the policy assessment and rulemaking components that complete the review.

The ISA, prepared by EPA's Office of Research and Development (ORD), National Center for Environmental Assessment (NCEA), provides a critical assessment of the latest available policy-relevant scientific information upon which the NAAQS are to be based. The ISA critically evaluates and integrates scientific information on the health and welfare effects associated with exposure to CO in ambient air. At this time, a first draft of the ISA and related Annexes (US EPA, 2009) has been released for CASAC review and public comment at an upcoming meeting (scheduled for May 12-13, 2009). The REA, to be prepared by EPA's Office of Air and Radiation (OAR), Office of Air Quality Planning and Standards (OAQPS), will draw from the information assessed in the ISA. The REA will focus on a quantitative assessment of exposure and dose metrics that are relevant to health effects of concern. The REA will include, as appropriate, quantitative estimates of human exposures and risks associated with recent ambient levels of CO, with levels simulated to just meet the current standards, and with levels simulated to just meet possible alternative standards.

[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.

This document describes the scope and methods planned for use in conducting the human health risk and exposure assessments to support the review of the primary (health-based) CO NAAQS. Since this document is being prepared early in the review process, prior to CASAC and public review of the first draft ISA (US EPA, 2009), it is appropriately general in nature. Nonetheless, it is intended to provide enough specificity to facilitate consultation with CASAC, as well as for public comment, in order to obtain advice on the overall scope, approaches, and key issues in advance of conducting analyses and presenting results in the first draft REA. The first draft ISA (US EPA, 2009) was used as the basis for the development of the approaches described below. This includes information on atmospheric chemistry, source emissions, air quality, human exposure, dosimetry and pharmacokinetics, and related health effects. CASAC consultation on this planning document coincides with its review of the first draft ISA (US EPA, 2009). CASAC and public comments on this document will be taken into consideration in the development of the first draft REA, the preparation of which will coincide with and draw from the second draft ISA. The second draft REA will draw on the final ISA and will reflect consideration of CASAC and public comments on the first draft REA. The final REA will take into consideration CASAC and public comments on the second draft REA. The final ISA and final REA will inform the policy assessment and rulemaking steps that will lead to proposed and final decisions on the CO NAAQS.

This introductory chapter includes a chronological description of events that mark the most significant milestones in the CO NAAQS reviews that have been conducted since 1971. Chapter 2 presents and overview of health effects evidence relevant to the planned assessments and the basic approach to risk characterization in this plan. Chapter 3 presents the approach for the planned exposure/dose analysis and for characterizing uncertainty and variability in the analysis. The schedule for completing these assessments is presented in Chapter 4.

1.1. Chronology of the CO NAAQS Reviews

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-hr average and 35 ppm, 1-hr average, neither to be exceeded more than once per year (36 FR 8186). In 1979, EPA published the Air Quality Criteria Document for Carbon Monoxide (1979 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 1979 AQCD, served as the basis for the development of the 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 (US 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 1991 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 was subsequently reviewed by CASAC and the public, and in a "closure 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 1991 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 at that time. Thus, the primary standards were retained at 9 parts per million (ppm), 8-hr average and 35 ppm, 1-hr average, neither to be exceeded more than once per year.

In 1997, revisions to the AQCD (US EPA, 1991) for the CO NAAQS were initiated and a workshop was held in September 1998 to review and discuss material to be contained in the revised AQCD. On June 9, 1999, CASAC held a public meeting to review the first draft AQCD and to provide a consultation on a draft exposure analysis methodology document. CASAC Panel members provided comments and suggestions for the exposure analysis methodology, including improvements for modeling indoor sources and ventilation rates, and calling on EPA to do more to address the overall uncertainty in the exposure/dose model. Comments from CASAC Panel members and the public on the AQCD 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 2000 AQCD (US EPA, 2000) was released in August 2000. EPA put on hold the NAAQS review when Congress requested that the National Research Council (NRC) review 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. 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 regarding management of CO air pollution, cold start emissions standards, oxygenated fuels, and CO monitoring. Following completion of this NRC report, EPA did not conduct rulemaking to complete the review.

EPA initiated the current review of the NAAQS for CO on September 13, 2007, with a call for information from the public (72 FR 52369) requesting the submission of recent scientific information on specified topics. A workshop was held on January 28–29, 2008 (73 FR 2490) to discuss policy-relevant scientific and technical information to inform EPA's planning for the CO NAAQS review. Following the workshop, a draft of EPA's Integrated Review Plan (IRP) ''Plan for Review of the National Ambient Air Quality Standards for Carbon Monoxide'' (US EPA, 2008a) was made available in March 2008 for public comment and was discussed by the CASAC via a publicly accessible teleconference consultation on April 8, 2008 (73 FR 12998). EPA made the final plan available in August 2008 (US EPA, 2008b). In November 2008, EPA held an authors' teleconference with invited scientific experts to discuss preliminary draft materials prepared during the ongoing development of the CO ISA and its supplementary Annexes. The first draft ISA (US EPA, 2009) for CO was made available for public review on March 12, 2009, and will be reviewed by CASAC concurrently with this Scope and Methods Plan at a meeting scheduled for May 12 and 13, 2009.

1.2. Overview of the Exposure/Dose Assessment analysis in Prior Reviews

Reviews of the CO NAAQS completed in 1985 and 1994 did not include quantitative health risk assessments. Rather, these reviews included analysis of exposure to ambient CO and associated internal dose in terms of carboxyhemoglobin (COHb) levels which were used to characterize risks in selected urban study areas. These prior risk characterizations compared the

numbers of at-risk individuals and percent of the at-risk population exceeding several potential health effect benchmarks, expressed in terms of COHb levels. This characterization was based on COHb levels observed in several controlled human exposure studies reporting aggravation of angina associated with short-term (< 8-hr) CO exposures.

Although the EPA did not complete the review initiated in 1997, OAQPS continued work on the CO exposure assessment to further develop the exposure assessment modeling component of the Total Risk Integrated Methodology (TRIM) system. A draft technical report (Johnson et al., 2000) was produced documenting the application of the CO exposure and dose modeling methodology for two study areas (Denver and Los Angeles). This report was subjected to an external peer review by three exposure modeling experts convened by Science Applications International Corporation (SAIC, 2001).

The methods used in this previous assessment, described below in chapter 3, form the bases for the analysis planned for this review. The planned analysis will also incorporate improvements made to the exposure model since the previous assessment.

2. HEALTH EFFECTS AND APPROACH TO RISK CHARACTERIZATION

The overall scope and approach to risk characterization for the current CO NAAQS review builds upon the methodology and analyses conducted in prior reviews of the CO standards. A brief summary of the health effects evidence and our provisional judgments about health effects endpoints to be included in the risk characterization is presented below in section 2.1, based on information in the first draft ISA. We note that the first draft REA will be informed by CASAC and public comment on this plan and review of the first draft ISA (US EPA, 2009), in addition to the information and evaluation contained in the second draft ISA and associated Annexes. The basic approach to risk characterization described in this plan reflects the availability of data from two different types of health studies: controlled human exposure studies and epidemiologic studies. Our plan to address the range of effects related to CO ambient exposures evaluated in the first draft ISA (US EPA, 2009) is organized based on the health effects supported by these two types of studies and is discussed below in sections 2.2 and 2.3, respectively.

2.1. Health Effects and Effects Levels

The mechanism of toxicity believed to be associated with health effects of greatest concern from CO exposure is hypoxia induced by elevated COHb levels. The primary exchange route for CO to human tissues is through the lungs. Although CO is a naturally occurring chemical in blood, being produced endogenously by normal catabolic processes, blood COHb levels do not often exceed 0.5 to 0.7 percent in healthy individuals unless exogenous CO is inhaled. Some individuals with high endogenous CO production can have COHb levels of 1.0 to 1.5 percent (e.g., people with anemia). Exogenous CO diffuses across the alveoli in the pulmonary region of the lung, entering the blood where it immediately binds with hemoglobin (Hb) to form COHb. Most healthy individuals can physiologically compensate for the resulting reduction in tissue oxygen (O_2) levels (e.g. through increased blood flow, blood vessel dilation) although the effect of reduced maximal exercise capacity has been reported in healthy persons even at low COHb levels (~3%). However, reduced delivery of O_2 is of heightened concern for individuals with ischemic heart diseases, since they have an already compromised O_2 delivery system to the heart muscle, which puts them at increased risk if exposed to CO.

The first draft ISA (US EPA, 2009) indicates that the integrative synthesis of the available evidence from controlled human exposure, epidemiologic, and toxicological studies suggests that a causal relationship is likely to exist between relevant short-term CO exposures and cardiovascular morbidity. The "most compelling evidence of a CO-induced effect on the cardiovascular system" comes from controlled exposure studies in humans with coronary artery disease (US EPA, 2009, sections 2.3.1 and 5.2). These studies, described in more detail in the 1991 and 2000 AQCDs, "demonstrate consistent decreases in the time to onset of exercise-induced angina and S-T segment changes at COHb levels ranging from 3-6 percent, with one multicenter study reporting similar effects at COHb levels as low as 2.4 percent" (US EPA, 2009, p.2-6). The first draft ISA (US EPA, 2009) also indicates that there are no human clinical studies published since the 2000 AQCD evaluating the effects of CO exposures resulting in COHb levels lower than 2.4 percent (US EPA, 2009, p.2-6).

A number of epidemiologic studies published since the 2000 AQCD and evaluated in the first draft ISA (US EPA, 2009) report associations between ambient CO concentrations and increased emergency department visits and hospital admissions for individuals suffering from cardiovascular disease. The 2000 AQCD concluded that epidemiologic studies provided evidence that short-term variations in ambient CO concentrations were associated with daily hospital admissions for heart disease. The first draft ISA (US EPA, 2009) builds on this conclusion. All but one of the recent epidemiologic studies was conducted in locations where the entire distribution of monitored CO concentrations were below the level of the current CO NAAQS (for details on the recent epidemiologic studies see US EPA, 2009, Table 5-7). In discussing the epidemiologic evidence, the first draft ISA (US EPA, 2009, p.5-45) notes that "it is difficult to determine from this group of studies the extent to which CO is independently associated with cardiovascular disease outcomes or if CO is a marker for the effects of another traffic-related pollutant or mix of pollutants." While acknowledging that this "complicates the efforts to disentangle specific CO-related health effects" the first draft ISA (US EPA, 2009) notes that CO associations generally remain robust in copollutant models, that the specific endpoints are coherent with human clinical and toxicologic evidence from studies conducted at higher concentrations, and that these considerations *"support a direct effect of short-term CO exposure on cardiovascular morbidity at ambient concentrations below the current NAAQS level."*

2.2. Approach to Risk Characterization for Cardiovascular-Related Health Effects Observed in Controlled Human Exposure Studies

As discussed above, there are a number of controlled human exposure studies reporting reduced time to onset of angina and other clinical cardiovascular measures in moderately exercising angina subjects who received short-term exposures to CO. As shown in Figure 2-1, there are statistically significant group mean responses, measured in terms of reduced time to onset of exercise-induced angina, observed in the range of 3 to 6 percent COHb (measured by CO-oximeter) in subjects with coronary artery disease. However, there is no clear pattern across the different studies with respect to the magnitude of the decreased time to onset of angina versus dose level. It is important to note that the results presented in Figure 2-1 have been compiled from individual studies with different study design and methodology (e.g., different exercise duration, methods used to measure COHb with different levels of accuracy, subject populations); therefore, comparisons must be interpreted with caution. In addition, these studies do not address the fraction of the population experiencing a specified health effect at various dose levels. Thus, based on information in the first draft ISA (US EPA, 2009), there does not appear at this time to be sufficient controlled human exposure data to support the development of quantitative dose-response relationships which would be required in order to conduct a quantitative risk assessment for this health endpoint.

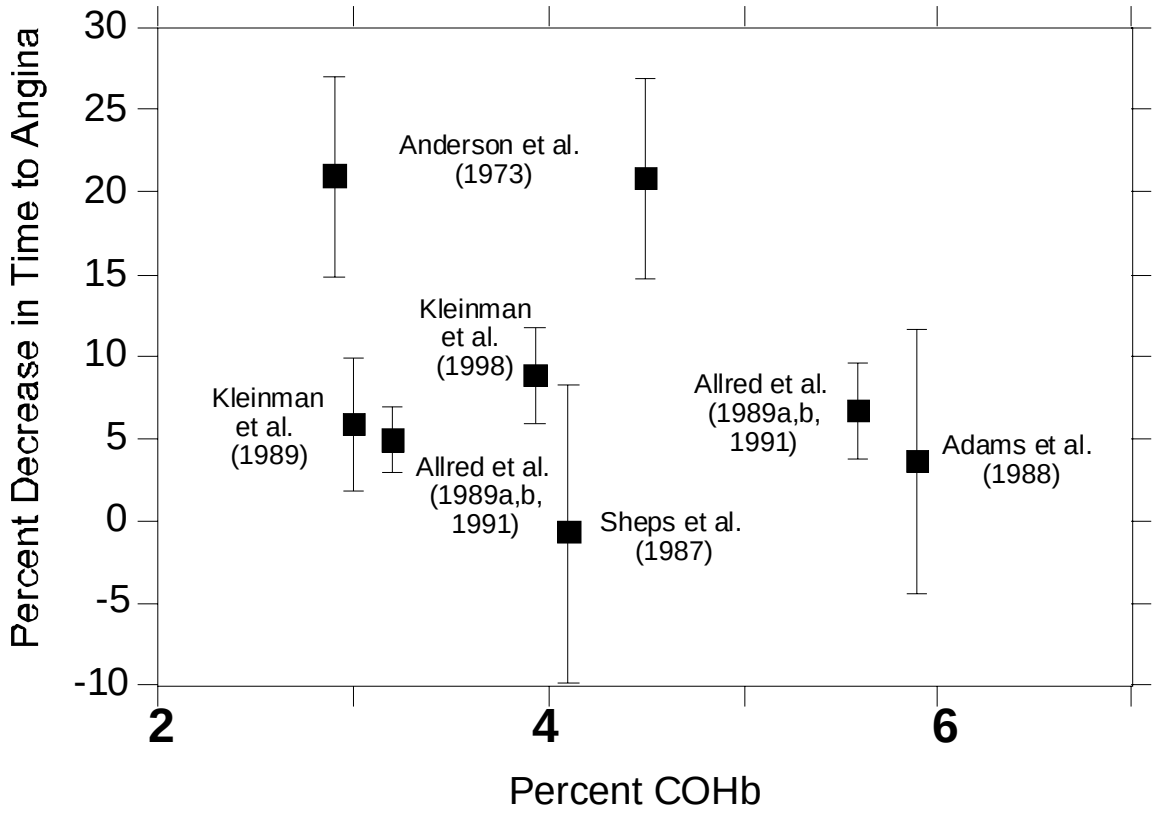

Figure 2-1. The Effect of CO Exposure on Time to Onset of Angina in Controlled Human Exposure Studies
For comparison across studies, data are presented as mean percent differences in COHb levels (CO-oximeter measurement) between air- and CO-exposure days for individual subjects calculated from each study. Bars indicate calculated standard errors of the mean.

Source: Adapted from the 2000 Air Quality Criteria for Carbon Monoxide (US EPA, 2000)

Similar to the approach used in prior CO NAAQS reviews, we plan to estimate CO exposures and resulting doses (i.e., COHb levels) and characterize risk for the population with cardiovascular disease in two urban study areas associated with CO levels representing recent air quality and air quality adjusted to simulate just meeting the current CO NAAQS and any potential alternative standards under consideration. Risk will be characterized using a potential health effect benchmark level approach. More specifically, we will estimate the number and percent of the population with cardiovascular disease that would exceed potential health effect

benchmark levels, derived from the evaluation of the controlled human exposure studies summarized above and specified in terms of COHb levels, upon just meeting various CO air quality scenarios.

Potential health benchmark values to be used in the planned risk characterization linked to the exposure/dose analyses will be derived solely based on the controlled human exposure literature. This is primarily because CO concentrations reported in controlled human exposure studies represent actual personal exposures rather than concentrations measured at fixed site ambient monitors. In addition, controlled human exposure studies can examine the health effects of CO in the absence of co-pollutants that can confound results in epidemiologic analyses; thus, health effects observed in controlled human exposure studies can confidently be attributed to a defined COHb dose level associated with ambient CO exposures.

In identifying the potential health effect benchmark levels, staff plan to use 2.0, 2.5 and 3.0 percent COHb for the risk characterization for the effects observed in cardiovascular disease patients reported in a number of controlled human exposure studies. This range captures the lowest adverse effect levels reported in most of the controlled human exposure studies reporting effects of CO on individuals with angina. While most of the early studies used CO-oximeters to measure COHb levels, later studies used gas chromatography (GC) as the method of measurement, which is widely considered to be more accurate. Comparisons summarized in the 1991 AQCD (US EPA, 1991) between CO-oximeter and GC measurements of COHb found that the CO-oximeter measurements could be either higher or lower, depending on the specific instrument and the measurement range, and were particularly variable at low COHb levels (< 5%).

As discussed in section 3.2, the calculation of dose (blood levels of COHb) for the exposure/dose modeling planned for this assessment is based on the well-established Coburn-Forster-Kane (CFK) equation (Coburn et al., 1965). We recognize that COHb estimates from the exposure/dose modeling are more appropriately compared to COHb levels measured using GC. The range of potential health effects benchmarks that we plan to use extends lower than the range where controlled human exposure studies reported CO-related health effects (i.e., 3-6 percent COHb with one multicenter study reporting effects at 2.4% COHb using GC) to take into consideration both the uncertainty about the actual COHb levels experienced in the controlled human exposure studies due to the use of different measurement methods and that these studies

did not include individuals with more severe cardiovascular disease who may respond at lower COHb levels relative to the subjects tested. Based on this consideration, staff believes that 2.0, 2.5, and 3.0 percent COHb are appropriate values for potential health effect benchmark levels to be included in the current CO risk characterization to address concerns about cardiovascular effects observed in a number of controlled human exposure studies.

The exposure and dose estimation will be conducted using EPA's APEX model (see section 3 for additional details). Counts will be estimated for the number of people and the total number of occurrences for which various potential health effect COHb benchmark levels are exceeded. We selected Denver and Los Angeles areas as exposure modeling areas of interest because they (1) have been included in prior CO NAAQS exposure assessments and thus serve as an important connection with past assessments, (2) they have historically had the highest elevated CO ambient concentrations among urban areas in the US, (3) Denver represents a high altitude city and the interaction of CO and high altitude is of interest, and (4) they are in the top four of the 10 urban areas evaluated in the ISA with at least 75 percent data completeness with respect to the maximum and 99th percentile 1- and 8-hr daily maximum CO concentrations.

2.3. Approach for Risk Characterization for Cardiovascular-related Health Effects Reported in Epidemiological Studies

In deciding whether or not to conduct a quantitative risk assessment for cardiovascular morbidity based on associations reported in community epidemiologic studies, we plan to take into account the following considerations: (1) whether the weight of the evidence supports conducting a quantitative assessment for specific health endpoints, (2) whether the data needed to conduct such quantitative assessments are available, (3) the anticipated utility of results to inform decisions on the adequacy of the current CO NAAQS and to provide insights related to potential alternative standards, and (4) whether there is adequate time to complete such assessments under the current court-ordered schedule.

As noted above, the first draft ISA (US EPA, 2009) evaluates epidemiologic findings from a group of studies, many of which were conducted since the 2000 CO AQCD (US EPA, 2000) that observed associations between ambient CO concentrations and increases in emergency department visits and hospital admissions for cardiovascular effects. All but one of

the recent epidemiologic studies were conducted in locations where the entire distribution of monitored CO concentrations was below the level of the current CO NAAQS. As noted previously in this document, uncertainty in evaluating the epidemiological evidence, specifically, whether the effects reported at relatively low ambient CO concentrations in these studies are causally related to CO or whether ambient CO levels are serving as a surrogate for one or more components of the overall traffic-related air pollutant mixture may preclude the use of this evidence in a quantitative risk assessment. Moreover, there are concerns about whether measurement error in epidemiological studies utilizing fixed site monitors, which are potentially a poor representation of personal exposures to CO that vary spatially and temporally, can influence the observed association between CO and cardiovascular effects. In staff's view whether the results of co-pollutant models (US EPA, 2009, Figure 5.5) provide sufficient evidence to support conducting a quantitative risk assessment for CO effects at ambient levels warrants further consideration in consultation with CASAC prior to EPA deciding whether to conduct an epidemiologically based quantitative risk assessment for cardiovascular-related hospital admissions or emergency department visits.

3. SCOPE AND APPROACH FOR POPULATION EXPOSURE/DOSE ANALYSIS

3.1. Previous Assessments

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 model outputs of interest were estimates of the number of person-days of exposure to various CO levels for various scenarios for adults with cardiovascular disease in Denver. Estimates also were made of the percentage of the cardiovascular heart disease population in Denver[2] that would exceed selected COHb levels one or more times per year under different scenarios. The estimates of COHb were derived by applying a modified version of the 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).

The analysis indicated that if the current 8-hr standard were just met, the proportion of the nonsmoking population with cardiovascular disease experiencing exposures at or above 9 ppm for 8 hrs decreased by an order of magnitude or more from existing CO levels, down to less than 1 percent of the total person-days in that population. Likewise, meeting the current 8-hr 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 relative to existing CO levels. Upon meeting the 8-hr 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 percentage of the at-risk population was estimated to exceed higher COHb percentages. The analysis also took into account that certain indoor sources (e.g., passive smoking, gas stove usage) contributed to total CO exposure but could not be effectively mitigated by setting more stringent ambient air quality standards.

Additional exposure analyses were planned in 1999 using the Denver and Los Angeles areas to provide estimates of CO exposures and resultant COHb levels for adults with

[2] It was estimated in the 1992 exposure analysis that there were about 36,800 non-smoking adults in Denver with diagnosed or undiagnosed (silent) ischemia.

cardiovascular disease in these 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 and it was one of the areas with the highest ambient CO levels in the country. 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 also planned to conduct the analyses for Los Angeles for several reasons: (1) it presented the largest potential public health burden due to its relatively higher ambient CO levels and potential population exposure; (2) an extensive monitoring network was available; and (3) availability of a study in Los Angeles of personal and indoor CO concentrations that potentially could be used to evaluate the model.

The primary target population in the 1999 analysis 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-hrs and people exceeding various COHb levels. Only the 8-hr 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 10, 1999. The CASAC Panel members provided a number of specific suggestions, including improving the algorithm for estimating inside vehicle exposures, differentiating between electronic and gas pilot lights for stoves, and using alveolar instead of inhaled ventilation rates in the physiological model. Since that time, these and other improvements to the model have been made, as described in the next section. The CASAC Panel members also suggested that the exposure analysis include additional information to address the

overall uncertainty in the model. This plan addresses this issue in section 3.4. As noted in section 1.1, subsequent to the CASAC consultation on the 1999 draft CO exposure methodology report, a draft technical report (Johnson et al., 2000) was produced documenting the application of the CO exposure and dose modeling methodology for Denver and Los Angeles. This report was developed as part of the EPA's efforts to improve its exposure modeling tools.[3] As described in more detail in sections 3.2 and 3.3 below, the planned exposure/dose assessment builds on the 1999 and 2000 CO exposure/dose modeling efforts for Denver and Los Angeles.

3.2. The Exposure/Dose Modeling

EPA's Air Pollutants Exposure (APEX) model (also referred to as the Total Risk Integrated Methodology/Exposure (TRIM.Expo) model) will be used in this analysis for the estimation of population exposures and resulting dose due to ambient CO levels. The EPA has developed APEX as a tool for estimating human population exposure to criteria and air toxic pollutants. APEX serves as the human inhalation exposure model within the Total Risk Integrated Methodology (TRIM) framework (Richmond et al., 2002; US EPA 2003).

Figure 3-1 provides a schematic overview of the APEX model. APEX simulates the movement of individuals through time and space and their exposure to a given pollutant in indoor, outdoor, and in-vehicle microenvironments. The model stochastically generates simulated individuals using census-derived probability distributions for demographic characteristics. The population demographics are from the 2000 Census at the tract level, and a national commuting database based on 2000 Census data provides home-to-work commuting flows between tracts. Any number of simulated individuals can be modeled, and collectively they represent a random sample of the study area population.

APEX has a flexible approach for modeling microenvironmental concentrations, where the user can define the microenvironments to be modeled and their characteristics. Typical indoor microenvironments include residences, schools, and offices. Outdoor microenvironments include near roadways, bus stops, and playgrounds. Inside cars, trucks, and mass transit vehicles are microenvironments which are classified separately from indoors and outdoors.

[3] This draft report was subjected to an external peer review by 3 exposure modeling experts convened by Science Applications International Corporation (SAIC, 2001).

Figure 3-1. Conceptual Model and Data Flow of APEX

APEX calculates the concentration in the microenvironment associated with each event in an individual's activity pattern to obtain event-specific exposures.

The concentrations in each microenvironment are calculated using either a factors or mass-balance approach, and the user specifies the probability distributions of the parameters that go into the concentration calculations (e.g., indoor-outdoor air exchange rates). These distributions can depend on the values of other variables in the model. For example, the distribution of air exchange rates in a home, office, or car depends on the type of heating and air conditioning present, which are also stochastic inputs to the model. The user can choose to keep the value of a stochastic parameter constant for the entire simulation (e.g., house volume), or can specify that a new value shall be drawn hourly, daily, or seasonally from specified distributions. APEX also allows the user to specify diurnal, weekly, or seasonal patterns for various microenvironmental parameters.

APEX was derived from the probabilistic NAAQS Exposure Model (pNEM) used in prior CO NAAQS exposure assessments as described in section 3.1. Since that time the model has been restructured, improved, and expanded to reflect conceptual advances in the science of exposure modeling and newer input data available for the model. A user's guide and technical support document describe the APEX model in detail (US EPA, 2008c,d). As discussed below, key improvements to algorithms include:

- replacement of the cohort approach with a probabilistic sampling approach focused on individuals,
- development of a flexible method for specifying distributions for probabilistic microenvironment parameters and other model inputs,
- enhancement with a new approach for construction of longitudinal activity patterns for simulated persons, and
- accounting for fatigue and oxygen debt after exercise in the calculation of ventilation rates.

Further major improvements to data input to the model are discussed below, which focus on:

- residential air exchange rates, and
- census and commuting data.

3.2.1. Improvements to Algorithms

The pNEM was based on cohorts of people, with each cohort treated collectively as a subgroup. APEX models individuals rather than cohorts, which allows APEX to address both intra- and inter-individual variability in human activities, inhalation rates, and dose uptake rates. The model randomly selects a sample of hypothetical individuals in an actual population database and simulates each individual's movements through time and space (e.g., at home, in vehicles) to estimate their exposure to the pollutant.

APEX simulates the variability in the factors affecting exposure, which is important for assessment of the distribution of population exposures and dose. It incorporates stochastic processes representing the natural variability of personal profile characteristics, activity patterns, and microenvironment parameters. APEX has been developed to provide the user with a large degree of flexibility in specifying the distributions for modeling these stochastic processes. There are 15 parametric distributions and a percentile-based distribution that can be used, which can be selected conditionally according to the values of other variables or sampled values from other distributions.

A key issue in exposure modeling is the construction of year-long activity sequences for individuals based on a cross-sectional activity data base of 24-hour records. The human activity data will be drawn from the most recent version of the Consolidated Human Activity Database (CHAD) (McCurdy et al., 2000; EPA, 2002), developed and maintained by the Office of Research and Development's (ORD) National Exposure Research Laboratory (NERL). The CHAD includes data from several surveys covering specific time periods at city, state, and national levels, with varying degrees of representativeness, providing more than 28,000 diary-days of activity data (compared to about 17,000 in the previous modeling effort). The typical subject in the time/activity studies in CHAD provided less than two days of diary data. For this reason, the construction of a season-long activity sequence for each individual requires some combination of repeating the same data from one subject and using data from multiple subjects. An appropriate approach should adequately account for the day-to-day and week-to-week repetition of activities common to individuals while maintaining realistic variability between individuals. The method in APEX for creating longitudinal diaries was designed to capture the

tendency of individuals to repeat activities, based on reproducing realistic variation in a key diary variable, which is a user-selected function of diary variables (Glen et al., 2008).

In addition to exposure, APEX models breathing rates based on the physiology of each individual and the activities performed. For each activity type in CHAD, a distribution is provided for a corresponding metabolic energy of work ratio, MET ratio (McCurdy, 2000). The MET ratio is a ratio of the rate of energy consumption for non-rest activities as compared to the resting rate of energy consumption. The MET ratios have less interpersonal variation than do the absolute energy expenditures. Based on age and gender, the resting metabolic rate, along with other physiological variables are determined for each individual as part of their anthropometric characteristics. Because the MET ratios are sampled independently from distributions for each diary event, it may be possible to produce time-series of MET ratios that are physiologically unrealistic. APEX employs a MET adjustment algorithm based on a modeled oxygen deficit to prevent such overestimation of MET and breathing rates. The relationship between the oxygen deficit and the applied limits on MET ratios are nonlinear and are derived from published data on work capacity and oxygen consumption (Isaacs et al., 2008).

3.2.2. Improvements to Model Input Data

Distributions of air exchange rates (AERs) for the indoor microenvironments will be developed using data from several studies, comprising a total of more than 6,000 AER measurements (EPA, 2007, Appendix A). We plan to develop distributions of AERs for the two study areas based on stratification of the data by season and presence or absence of an air conditioner, as well as by geographic location.

To ensure that individual's daily activities are accurately represented within APEX, it is important to integrate working patterns into the assessment. The APEX tract-level commuting data are derived from the 2000 Census and collected as part of the Census Transportation Planning Package (CTPP). CTPP contains tabulations by place of residence, place of work, and the flows between the residence and work. These data are available from the U.S. Department of Transportation, Bureau of Transportation Statistics (U.S. Department of Transportation and U.S. Census Bureau, 2000). This database was not available for the previous modeling effort.

3.2.3. The COHb Model

Since COHb levels are a biomarker for the health effects of ambient-level exposures to CO and are used as an bioindicator of CO exposure, the focus of the exposure/dose assessment is on estimating COHb levels which can be related to potential health effect benchmarks as described in section 2.1. Therefore, the relationship between COHb and exposure to ambient CO levels is critical to the characterization of health risks associated with various CO air quality scenarios.

Dose (blood levels of COHb) is calculated based on the estimated exposures, estimated alveolar ventilation rate, and other physiological parameters for each simulated individual. The calculation of dose is based on the well-established CFK equation (Coburn et al., 1965), and has been used for many years by EPA and others to model COHb formation (see for example, Richmond and Johnson, 2000). This is a mechanistic model that uses physical and physiological processes and an understanding of biological processes to predict COHb levels resulting from CO exposures. The literature discusses linear and non-linear forms of the CFK equation. The linear form is an approximation that allows an explicit solution, but is not accurate under all conditions. The non-linear form is considered to be more physiologically correct and is the one implemented in APEX, taking into account exertion level and a variety of physiological parameters (e.g., lung diffusivity, endogenous CO production rate, Hb level, blood volume) (US EPA, 2008b). The CFK model is well accepted and has been evaluated using measured CO and COHb and has been shown to provide a good approximation to the COHb level at a steady level of inhaled exogenous CO (US EPA, 2009, page 4-2; US EPA, 2000, section 5.5.1).

3.3. Current Approach for Exposure and Dose Modeling

The exposure/dose assessment for the current review of the primary CO NAAQS is designed to estimate human exposures and dose and to characterize the potential health risks that are associated with recent 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 exposure/dose assessment draws upon the information presented in the draft ISA and its Annexes, the previous AQCDs for CO (US EPA, 1991, 2000), and the 1999 and 2000 draft exposure analysis reports (Johnson et al., 1999, 2000) and subsequent improvements to the exposure model in developing the CO exposure/dose assessment. This includes

information on atmospheric chemistry, air quality, human exposure, formation of blood COHb levels, and health effects of concern. The goals of the CO exposure/dose assessment are: (1) to develop estimates of blood COHb levels in sensitive populations resulting from exposure to CO for various CO air quality scenarios noted above; (2) to estimate the number of people and the total number of occurrences for which potential health effect COHb benchmark levels are exceeded for various CO air quality scenarios noted above; and (3) to identify key assumptions and uncertainties in the exposure and dose estimates.

The general approach is to estimate population exposures to ambient CO in two urban areas in the U.S., Denver, CO and Los Angeles, CA. These areas were selected since they have been previously modeled for CO exposures using the pNEM model. These two urban areas continue to be in the top urban areas evaluated in the first draft ISA with relatively complete data with respect to daily maximum 1- and 8-hr CO concentration levels. These two urban areas continue to also exhibit relatively higher CO ambient concentrations than other urban areas as shown in the draft ISA.

In the first draft REA, exposure and dose estimates for the general population and the population with cardiovascular disease for these areas will be generated for recent CO levels, based on a recent 3-year period, and for levels adjusted to just meet the current NAAQS. Exposures and dose would be modeled for any potential alternative CO standards in the second draft REA, based on adjusting the air quality data. An exposure analysis technical support document with a detailed description of the methodology and results will accompany the draft REA.

3.3.1. Specification of Microenvironments

The first step in the exposure/dose assessment will be to update the parameter distributions from the 2000 application for the mass balance and factors approaches for the calculation of microenvironmental concentrations in APEX. For this modeling application, we propose modeling the microenvironments listed in Table 3-1.

Table 3-1. Microenvironments to be Modeled

Microenvironment	Method
Indoors – residence	mass balance
Indoors – restaurants, bars	mass balance
Indoors – schools	mass balance
Indoors – day care centers (commercial)	mass balance
Indoors – other (e.g., offices, shopping)	mass balance or factors
Outdoors – bus stop	factors
Outdoors – near road	factors
Outdoors – other (e.g., playgrounds, parks)	factors
In vehicle – cars and light trucks	mass balance or factors
In vehicle – heavy trucks	mass balance or factors
In vehicle – school buses	mass balance or factors
In vehicle – mass transit vehicles	factors

We plan to calculate the concentrations in each microenvironment using either a factors or mass-balance approach, depending upon data availability, with probability distributions for the input parameters used in the calculations (e.g., indoor-outdoor air exchange rates) supplied as inputs to the model. These distributions represent the variability of parameters, and can vary spatially and can be set up to depend on the values of other variables in the model.

3.3.2. Population Demographics

We plan to obtain tract-level population counts from the 2000 Census of Population and Housing Summary File 1.[4] Summary File 1 (SF 1) contains the 100-percent data, which is the information compiled from the questions asked of all people and about every housing unit. In the 2000 U.S. Census, estimates of employment were developed by census tract.[5] The file input to APEX will be broken down by gender and age group, so that each gender/age group combination is given an employment probability fraction (ranging from 0 to 1) within each census tract. The age groupings in this file are: 16-19, 20-21, 22-24, 25-29, 30-34, 35-44, 45-54,

[4] http://www.census.gov/prod/cen2000/doc/sf1.pdf
[5] Employment data from the 2000 Census can be found on the U.S. Census web site: http://www.census.gov/population/www/cen2000/phc-t28.html (Employment Status: 2000- Supplemental Tables).

55-59, 60-61, 62-64, 65-69, 70-74, and greater than 75 years of age. Children under 16 years of age will be assumed to be not employed.

3.3.3. Commuting

As part of the population demographics inputs, it is important to integrate commuting patterns into the assessment for workers. In addition to using estimates of employment by tract, APEX also incorporates home-to-work commuting data. We plan to use the national commuting database provided with APEX in this analysis. Commuting data were derived from the 2000 Census and were collected as part of the Census Transportation Planning Package (CTPP) (U.S. DOT, 2000).[6] The data used to generate APEX inputs were taken from the "Part 3-The Journey To Work" files. These files contain counts of individuals commuting from home-to-work locations at a number of geographic scales. These data have been processed to calculate fractions for each tract-to-tract flow to create the national commuting data distributed with APEX. This database contains commuting data for each of the 50 states and Washington, D.C. This data set does not differentiate people that work at home from those that commute within their home tract.

3.3.4. Ambient CO Concentrations

We plan to estimate ambient CO concentrations using the same methodology used in the previous CO exposure modeling analysis and update the data underlying the methodology to the extent that more recent data are available.

In the previous pNEM/CO application (see Johnson et al., 2000), outdoor concentrations were estimated from the relationship

$$C^{O}_{mdt} = M_m \, L_{md} \, T_{mdt} \, C_{dt}^{0.621} \qquad (1)$$

where *d* is a monitor index, *m* is a microenvironment index, *t* is a time index (hourly), and 'district *d*' refers to the geographic area of influence of monitor *d*; i.e., the outdoor

[6] These data are available from the U.S. DOT Bureau of Transportation Statistics (BTS) at the web site: http://transtats.bts.gov/.

concentrations for microenvironments in the geographic district *d* are estimated using concentrations measured at monitor *d*.

C^{O}_{mdt} = the estimated outdoor CO concentration with respect to microenvironment *m* in district *d* at time *t*,

M_m = constant multiplier (> 0) specific to microenvironment *m* (Table 3-2),

L_{md} = location multiplier randomly selected from a lognormal distribution with geometric mean equal to 1.0 and geometric standard deviation equal to 1.52, for each microenvironment *m*, and district *d* (held constant for all hours),

T_{mdt} = time-of-day multiplier randomly selected from a lognormal distribution with geometric mean equal to 1.0 and geometric standard deviation equal to 1.63, for each microenvironment *m*, district *d*, time *t*, and

C_{dt} = the CO concentration measured at monitor *d* at time *t*.

The development of equation 1 was based on data from a California residential exposure study conducted by Wilson, Colome, and Tian (1995) together with data provided by the Denver Personal Monitoring Study (Akland et al, 1985; Johnson, 1984). The parametric distributions for ***L*** and ***T*** were estimated by analyzing data obtained from the California residential study, which measured 10-minute CO concentrations outside 156 residences, 70 from Los Angeles and 86 from San Diego This yielded a database of 6,330 hourly average concentrations, which were compared with the hourly CO concentrations measured simultaneously at the nearest fixed-site monitor.

The values of the microenvironment-specific parameter ***M*** were estimated by an analysis of data from the Denver Study. During this study, each of approximately 450 subjects carried a personal exposure monitor (PEM) for two 24-hour periods. Each PEM measured CO concentration continuously. The PEM readings were averaged by exposure event such that each event was associated with a single microenvironment and a single hour. Event durations ranged from one minute to one hour. The microenvironment assigned to each PEM reading was determined from entries made in a real-time diary carried by the subject.

Equation 1 estimates the outdoor CO concentration associated with a particular microenvironment *m*, even when the microenvironment is an indoor location. Few of the outdoor PEM values reported by the Denver study could be reliably associated with particular indoor microenvironments. Consequently, a simplified procedure was employed for estimating

the values of ***M***, assuming that the mean of the indoor PEM values for each indoor microenvironment was approximately equal to the mean of the outdoor concentration associated with that indoor microenvironment.

Table 3-2. Estimated Values of the Parameter M in Equation 1

Microenvironment		M
Indoors	Residence	1.034
Indoors	Auto service station	2.970
Indoors	Health care facility, School, Church, Manufacturing facility	0.989
Indoors	Other locations	1.213
Outdoors	Near road, Bicycle, Motorcycle	1.607
Outdoor	Indoor parking garage, Outdoor parking garage, Outdoor parking lot, Outdoor service station	2.970
Outdoors	Other locations	1.436
Vehicle	Automobile, Truck, Bus, Train, Subway, Other vehicle	3.020

Source: Johnson et al., 2000.

3.3.5. Air Quality Adjustment to Meet Standards

There are many possible ways to create characterizations of air quality to represent scenarios "just meeting" the current and any potential alternative CO standards. Previous reviews have used a proportional adjustment method which decreased CO levels on all days by the same percentage at all monitors in a given area. The percentage amount of adjustment is just enough so that neither the 1-hr nor the 8-hr levels of the standards under consideration are exceeded. Generally, the amount of adjustment required to just meet the 1-hr and 8-hr levels will not be the same, so, in practice, this procedure brings the design value for one of the two averaging times to be equal to the level of the corresponding standard, while the design value of the other averaging time would be reduced to a level below the standard. In this review, we will again evaluate the appropriateness of the proportional adjustment approach by comparing it with historical changes in distributions of CO concentrations in selected locations. In this review, the

required adjustment will result in an increase of CO levels to simulate just meeting the current standards.

3.3.6. Indoor Sources

The indoor sources of CO that will be modeled are emissions from gas stoves for cooking and the contribution of passive smoking indoors ("environmental tobacco smoke," or ETS). A review of the scientific literature for other indoor sources (e.g., kerosene space heaters, gas space heaters, wood stoves, fireplaces, and attached garages) will be conducted to ascertain whether emissions from these sources can be adequately characterized by available data. As in prior assessments, we plan to present CO exposure and dose both including and excluding indoor sources. The primary focus for the CO NAAQS review is on the ambient contribution to exposures and dose.

The resulting exposure analysis will provide estimates of CO exposure and their associated COHb levels for population living in the selected urban areas. It is recognized that there are significant uncertainties associated with the resulting exposure and dose estimates, and these uncertainties must be taken into account in assessing the utility of the exposure analysis. The next section discusses the planned approach for assessing these uncertainties

3.4. Characterization of Uncertainty and Variability

An important issue associated with any population exposure and/or dose assessment is the characterization of uncertainty and variability.

Variability refers to the heterogeneity in a population or variable of interest that is inherent and cannot be reduced through further research. This variability may be due to differences in population (e.g., age distribution), population activities that affect exposure to CO (e.g., proximity to roadways), levels of CO, and/or other factors that vary either within or across urban areas.

Uncertainty refers to the lack of knowledge regarding both the actual values of model input variables (parameter uncertainty) and the physical systems or relationships (model uncertainty – e.g., the relationship between ambient CO concentrations and CO concentrations measured at fixed site monitors). In any exposure analysis, uncertainty is, ideally, reduced to the maximum extent possible, through improved measurement of key parameters and ongoing

model refinement. However, significant uncertainty often remains and emphasis is then placed on characterizing the nature of that uncertainty and its impact on exposure and dose estimates. The characterization of uncertainty can include both qualitative and quantitative analyses, the latter requiring more detailed information. The goal for addressing variability is to incorporate the sources of variability into the model to ensure that the estimates of exposure and dose reflect the variability of exposure and dose across the study population. Our approach to variability is outlined in section 3.4.1.

The planned approach for evaluating uncertainty is adapted from guidelines outlining how to conduct a qualitative uncertainty characterization for exposure assessment (WHO, 2008). First, the key sources of the assessment that contribute to uncertainty are identified, and the rationale for why they are included is discussed. Second, a qualitative characterization for the types and components of uncertainty is carried out using sensitivity analysis. This results in a summary describing, for each source of uncertainty, an indication of the potential bias direction, and an assignment of the uncertainty to low, medium, and high categories. Third, a limited quantitative assessment of uncertainty is performed for selected sources of uncertainty. Our qualitative and quantitative approaches to characterizing uncertainty are addressed in sections 3.4.2 and 3.4.3.

3.4.1. Addressing Variability

APEX has been designed to enable incorporation of variability of almost all of the input data and parameters, including the physiological parameters which are important input parameters to the CFK equation. As a result, APEX addresses much of the variability in the exposure and dose estimates resulting from the variability of the factors affecting human exposure and dose. The following model inputs and parameters have probability distributions representing variability:

- Population - Random samples from Census tracts, by age, gender, race
- Activity patterns - Stratified samples from CHAD
- Commuting - Random samples from Census tracts
- Employment - Random samples from Census tracts, by age and gender
- Ambient pollutant concentrations (spatial and temporal variability)
- Ambient meteorological data (spatial and temporal variability)

- Physiology relevant to estimating alveolar ventilation rate: body mass, resting metabolic rate, maximum level of sustained metabolic activity, oxygen uptake per unit of energy expended, and metabolic equivalents by activity (METS)
- Physiology relevant to estimating COHb levels: blood volume, lung diffusivity, endogenous CO production rate, and amount of Hb in the blood
- Coefficients of regression equations for ventilation rates
- Coefficients of regression equations for resting metabolic rates
- Coefficients of regression equations for body surface area
- Coefficients of regression equations for height
- Air exchange rates
- Decay and deposition rates
- Penetration factors
- Proximity factors
- Volumes of microenvironments
- Indoor source emission rates
- Air conditioning prevalence rates

3.4.2. Uncertainty Characterization – Qualitative Assessment

We plan to include a qualitative discussion of uncertainty in the exposure and dose assessment, starting with identification and description of key sources of uncertainty, and a list of secondary sources of uncertainty. This will be followed with an analysis of the sensitivity of the model output (estimated distributions of exposure and dose) to each of the individual factors (input data and parameters) contributing to uncertainty. A local sensitivity analysis will be performed, varying the one at a time factors by five percent of their nominal values and running APEX with all other parameters at their nominal values. Since most of the inputs to APEX are specified as parametric distributions (of variability), it is the parameters of these distributions that will be varied. In a few cases, correlation between parameters may exist where pairs of parameters may have to be simultaneously varied if the value of one parameter constrains the other. The sensitivity and elasticity[7] will be calculated and tornado graphs will be used to present the results of this sensitivity analysis. These graphs are particularly useful in illustrating which factors have a potentially higher impact on the exposure and dose results and how all the factors rank as to influencing those results and in which direction (positively or negatively).

This local analysis will be supplemented with a global sensitivity analysis, where the sensitivity involves the study of the exposure model behavior over the entire range of exposure

[7] See Appendix A for definitions of *Sensitivity* and *Elasticity*.

parameter variation and investigating their impact on the overall result. We will calculate the sensitivity score[8] for model inputs for which we can identify ranges of potential variation. The advantage of the sensitivity score is that it differentiates between precise (well-known) inputs with high sensitivity and imprecise inputs with high sensitivity: this measure will be larger if the input is less precisely known (keeping sensitivity the same). These are the inputs with the potential for large impacts on model output uncertainty. This will allow for their ranking in order to prioritize our focus on the most important ones.

These analyses of model sensitivity will support a qualitative discussion of uncertainties and a qualitative assessment of the particular sources of uncertainty in terms of their potential impact on exposure and dose levels using "high," "medium," and "low" designations.

3.4.3. Uncertainty Characterization – Quantitative Analysis

The primary difficulty in performing quantitative uncertainty analysis is how to appropriately characterize the uncertainties of the model inputs and formulation when faced with limited data. Information about the variability of model inputs or the variability and uncertainty combined is often available, but it is usually difficult to estimate the uncertainty separately from the variability.

Based on previous analyses of uncertainties of exposure modeling (Langstaff, 2007), we expect the following to be influential sources of uncertainty associated with modeling CO population exposure and dose:

- In representing the significant spatial and temporal gradients in ambient CO concentrations relative to fixed-site CO concentrations, in particular, CO concentrations near roadways.
- In portraying behavior (activity patterns and energy expenditures) related to CO exposure and dose (e.g., amount of time spent in high CO microenvironments, outdoor activities). There are not much activity data in CHAD that are relatively recent and based on surveys in Denver and Los Angeles. Therefore the activity data used in this modeling effort may not be representative of the cities and time periods to be modeled.

[8] See Appendix A.

- In estimating air exchange rates indoors and in vehicles. AERs are the most important determinant in the relationship between outdoor concentrations and the concentrations in indoor and in-vehicle microenvironments.

The sensitivity analyses described above will be carried out for each of these sources of uncertainty. The algorithm for estimating outdoor concentrations, described in section 3.3, will be evaluated by comparing its predictions with monitored CO concentrations. In the absence of the data required to support a comprehensive 2-dimensional probabilistic uncertainty analysis that treats both uncertainty and variability of all of the model inputs, a limited 2-dimensional probabilistic analysis will be conducted to support quantitative characterization of uncertainty. For the factors judged to have a major impact on the overall uncertainty of the estimated exposure and dose, a literature search will be conducted to identify ranges of uncertainty for each of the factors and the limited quantitative probabilistic analysis will be carried out for these model inputs.

4. SCHEDULE OF KEY MILESTONES

Table 4-1 lists the key milestones for the Risk and Exposure Assessment (REA) that are planned as part of the current CO NAAQS review. Consultation with the CASAC CO Panel is scheduled for May 12-13, 2009 to obtain review of the first draft Integrated Science Assessment (US EPA, 2009) and to obtain input on the plans to conduct quantitative assessments. EPA staff will then proceed to develop estimates of CO exposures and resulting doses (i.e., COHb levels) for the population with cardiovascular disease in two urban study areas associated with CO levels representing recent air quality and air quality adjusted to simulate just meeting the current CO NAAQS, and any potential alternative standards under consideration. These estimates and the methodologies used will be presented in the first draft CO REA. CASAC and public comments on this plan will be taken into consideration in the development of the second draft REA, the preparation of which will coincide and draw from the second draft ISA. The first draft REA is scheduled to be released for CASAC and public review on October 29, 2009. EPA will receive comments on this draft document from the CASAC and the general public at a meeting planned for November 2009. The second draft REA will draw on the final ISA and will reflect consideration of CASAC and public comments on the first draft REA. The second draft REA will include assessments for just meeting potential alternative standards. We plan to release the second draft REA in February 2010 for review by CASAC and the general public at a meeting that is planned for March 2010. Staff will consider these review comments and prepare a final REA, to be completed by May 28, 2010. The final REA will reflect consideration of CASAC and public comments on the second draft REA. The final ISA and final REA will inform the policy assessment and rulemaking steps that will lead to a final decision of the CO NAAQS. 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), which requires EPA to sign proposed and final rules by October 28, 2010 and May 13, 2011, respectively.

Table 4-1. Key Milestones for the Risk and Exposure Assessments

Milestones	Date
First draft CO ISA	March 12, 2009*
Release CO REA Scope and Methods Plan	April 2009
CASAC/public review and meeting on first draft CO ISA	May 12-13, 2009
CASAC consultation on CO REA Scope and Methods Plan	May 12-13, 2009
Release second draft CO ISA	September 2009
Release first draft CO REA	October 29, 2009*
CASAC/public review and meeting on second draft CO ISA and first draft REA	November 2009
Final CO ISA	January 29, 2010*
Release second draft of the CO REA	February 2010
CASAC/public review and meeting on second draft CO REA	March 2010
Final CO REA	May 28, 2010*

* Court-ordered deadline dates.

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United States Environmental Protection Agency	Office of Air Quality Planning and Standards Air Quality Strategies and Standards Division Research Triangle Park, NC	Publication No. EPA 452/R-09-004 April 2009

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