

Chapter 1. Introduction

The Integrated Science Assessment (ISA) is a concise evaluation and synthesis of the most policy-relevant science for reviewing the national ambient air quality standards (NAAQS). Because the ISA communicates critical science judgments relevant to the NAAQS review, it forms the scientific foundation for the review of the NAAQS for carbon monoxide (CO). The existing primary CO standards include a 1-hour (h) average (avg) standard set at 35 parts per million (ppm), and an 8-h avg standard set at 9 ppm, neither to be exceeded more than once per year. There is currently no secondary standard for CO.

The ISA accurately reflects “the latest scientific knowledge useful in indicating the kind and extent of identifiable effects on public health which may be expected from the presence of [a] pollutant in ambient air” (42 U.S.C. 7408). Key information and judgments formerly contained in the Air Quality Criteria Document (AQCD) for CO are incorporated in this assessment. Additional details of the pertinent scientific literature published since the last review, as well as selected older studies of particular interest, are included in a series of annexes. This ISA thus serves to update and revise the evaluation of the scientific evidence available at the time of the previous review of the NAAQS for CO that was completed in 2000.

The integrated *Plan for Review of the National Ambient Air Quality Standards for Carbon Monoxide* (U.S. EPA, 2008, [193995](#)) identifies key policy-relevant questions that provide a framework for this assessment of the scientific evidence. These questions frame the entire review of the NAAQS for CO and thus are informed by both science and policy considerations. The ISA organizes, presents, and integrates the scientific evidence which is considered along with findings from risk analyses and policy considerations to help the U.S. Environmental Protection Agency (EPA) address these questions during the NAAQS review. In evaluating the health evidence, the focus of this assessment is on scientific evidence that is most relevant to the following questions taken directly from the Integrated Review Plan:

- 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? 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, multiday distributed lags)?

Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at <http://epa.gov/hero>. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISAs) and the Integrated Risk Information System (IRIS).

- 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?
- 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?

1.1. Legislative Requirements

Two sections of the Clean Air Act (CAA, the Act) govern the establishment and revision of the NAAQS. Section 108 of the Act (42 U.S.C. 7408) directs the Administrator to identify and list “air pollutants” that “in [her] judgment, 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 (42 U.S.C. 7408). 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...” 42 U.S.C. 7408(b).

Section 109 of the Act (42 U.S.C. 7409) directs the EPA Administrator to propose and promulgate “primary” and “secondary” National Ambient Air Quality Standards (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.”¹ 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 U.S. EPA Administrator, based on such criteria, is required to protect the public welfare from any known or anticipated adverse effects associated with the presence of [the] pollutant in the ambient air.”² 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). The aforementioned 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 susceptible population(s), and the kind and degree of the uncertainties that must be addressed. The selection of any particular approach to providing an

¹ The legislative history of section 109 of the Clean Air Act indicates that a primary standard is to be set at “the maximum permissible ambient air level . . . which will protect the health of any [sensitive] group of the population,” and that for this purpose “reference should be made to a representative sample of persons comprising the sensitive group rather than to a single person in such a group” [S. Rep. No. 91-1196, 91st Cong., 2d Sess. 10 (1970)].

² 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.”

adequate margin of safety is a policy choice left specifically to the Administrator's judgment. See *Lead Industries Association v. EPA*, supra, 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 *Whitman v. American Trucking Associations*, 531 U.S. 457, 465-472, 475-76 (D.C. Cir. 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 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 1980s, this independent review function has been performed by the Clean Air Scientific Advisory Committee (CASAC) of EPA's Science Advisory Board (SAB).

1.2. History of the NAAQS for CO

On April 30, 1971, EPA promulgated identical primary and secondary NAAQS for CO, under Section 109 of the Clean Air Act, set at 9 ppm, 8-h avg and 35 ppm, 1-h avg, 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, [017687](#)), which updated the scientific criteria upon which the initial CO standards were based. A Staff Paper (U.S. EPA, 1979, [194665](#)) was prepared and, along with the AQCD (1979, [017687](#)), 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 announcing a second public comment period (47 FR 26407). Following substantial reexamination of the scientific data, EPA prepared an Addendum to the 1979 AQCD (1984, [012690](#)) and an updated Staff Paper (1984, [012691](#)). 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 subsequently released a revised AQCD (U.S. EPA, 1991, [017643](#)) for CASAC and public review. In a "closure letter" (McClellan, 1991, [194666](#)) sent to the Administrator, the CASAC concluded that the AQCD (U.S. EPA, 1991, [017643](#)) "... 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 letter" (McClellan, 1992, [194667](#)) sent to the Administrator, CASAC 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 (U.S. EPA, 1991, [017643](#)) and staff conclusions and recommendations contained in the revised Staff Paper (U.S. EPA, 1992, [084191](#)), 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.

In 1997, revisions to the 1991 AQCD (U.S. EPA, 1991, [017643](#)) were initiated. A workshop was held in September 1998 to review and discuss material contained in the revised draft 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 (U.S. EPA, 2000, [000907](#)) 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 (National Research Council, 2003, [042550](#)) 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 NAAQS review which started in 1997.

1.3. ISA Development

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). In addition to the call for information, publications were identified through an ongoing literature search process that includes extensive computer database mining on specific topics. Literature searches were conducted routinely to identify studies published since the last review, focusing on publications from 1999 to May 2009. Search strategies were iteratively modified to optimize identification of pertinent publications. Additional papers were identified for inclusion in several ways: review of pre-publication tables of contents for journals in which relevant papers may be published; independent identification of relevant literature by expert authors; and identification by the public and CASAC during the external review process. Publications considered for inclusion in the ISA were added to the Health and Environmental Research Online (HERO) database recently developed by EPA (<http://cfpub.epa.gov/ncea/hero/>); note that all references in the ISA include a HERO ID that provides a link to the database. Typically, only information that had undergone scientific peer review and had been published or accepted for publication was considered, along with analyses conducted by EPA using publicly available data. This review has attempted to evaluate all relevant data published since the last review pertaining to the atmospheric science of CO, human exposure to ambient CO, and epidemiologic, controlled human exposure, and animal toxicological studies on CO, including those related to exposure-response relationships, mode(s) of action (MOA), or susceptible populations. Added to the body of research on CO effects were EPA's analyses of air quality and emissions data, studies on atmospheric chemistry, transport, and fate of these emissions, as well as issues related to exposure to CO. An extensive literature search for data on the ecological effects of ambient CO did not identify any relevant information published since the review of the ecological effects evidence in the 1979 CO AQCD (U.S. EPA, 1979, [017687](#)).

In general, in assessing the scientific quality and relevance of health and environmental effects studies, the following considerations have been taken into account when selecting studies for inclusion in the ISA or its annexes. The selection process for studies included in this ISA is shown in Figure 1-1.

- Are the study populations, subjects, or animal models adequately selected and are they sufficiently well defined to allow for meaningful comparisons between study or exposure groups?
- Are the statistical analyses appropriate, properly performed, and properly interpreted? Are likely covariates adequately controlled or taken into account in the study design and statistical analysis?
- Are the air quality data, exposure, or dose metrics of adequate quality and sufficiently representative of information regarding ambient CO?
- Are the health or welfare effect measurements meaningful and reliable?

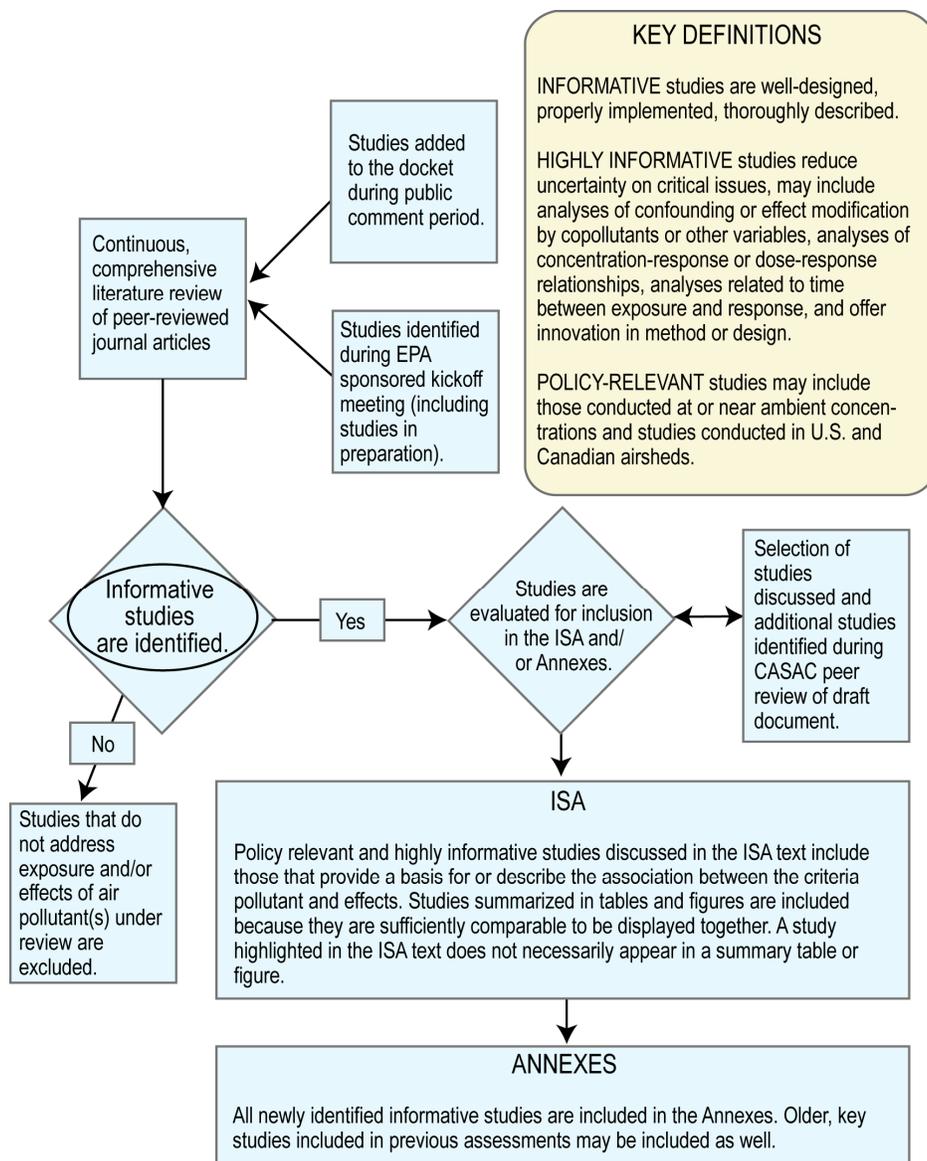


Figure 1-1. Identification of studies for inclusion in the ISA.

In selecting epidemiologic studies, EPA considered whether a given study presented information on associations with short- or long-term CO exposures at or near ambient levels of CO; considered approaches to evaluate issues related to potential confounding by other pollutants; assessed potential effect modifiers; addressed health endpoints and populations not previously extensively researched; and evaluated important methodologic issues (e.g., lag or time period between exposure and effects, model specifications, thresholds, mortality displacement) related to interpretation of the health evidence. Among the epidemiologic studies selected, particular emphasis was placed on those studies most relevant to the review of the NAAQS. Specifically, studies conducted in the United States (U.S.) or Canada were discussed in more detail than those from other geographical regions. Particular emphasis was placed on: (1) recent multicity studies that employ standardized analysis methods for evaluating effects of CO and that provide overall estimates for effects based on combined analyses of information pooled across multiple cities; (2) studies that help understand quantitative relationships between exposure concentrations and effects; (3) new studies that provide evidence on effects in susceptible populations; and (4) studies that consider and report CO as a component of a complex mixture of air pollutants.

Criteria for the selection of research evaluating controlled human exposure or animal toxicological studies included a focus on studies conducted using relevant pollutant exposures. For both types of studies, relevant pollutant exposures are considered to be those generally within one or two orders of magnitude of ambient CO concentrations. Studies in which higher doses were used may also be considered if they provide information relevant to understanding MOAs or mechanisms, as noted below.

Evaluation of controlled human exposure studies focused on those that approximated expected human exposure conditions in terms of concentration and duration. In the selection of controlled human exposure studies, emphasis is placed on studies that (1) investigate potentially susceptible populations such as people with cardiovascular diseases; (2) address issues such as concentration-response or time-course of responses; (3) include control exposures to filtered air; and (4) have sufficient statistical power to assess findings.

Review of the animal toxicological evidence focused on studies that approximate expected human dose conditions, which will vary depending on the toxicokinetics and biological sensitivity of the particular laboratory animal species or strains studied. Due to resource constraints on exposure duration and numbers of animals tested, animal studies typically utilize high-concentration exposures to acquire data relating to mechanisms and assure a measureable response. Such studies were considered to the extent that they provided useful information to inform our understanding of interspecies differences and potential sensitivity differences between healthy and susceptible human populations.

These criteria provide benchmarks for evaluating various studies and for focusing on the policy-relevant studies in assessing the body of health and welfare effects evidence. Detailed critical analysis of all CO health and welfare effects studies, especially in relation to the above considerations, is beyond the scope of this document. Of most relevance for evaluation of studies is whether they provide useful qualitative or quantitative information on exposure-effect or exposure-response relationships for effects associated with current ambient air concentrations of CO that can inform decisions on whether to retain or revise the standards.

In developing the CO ISA, EPA began by reviewing and summarizing the evidence on atmospheric sciences and exposure and the health effects evidence from in vivo and in vitro toxicological studies, controlled human exposure studies, and epidemiologic studies. In November 2008, EPA invited EPA staff and other researchers with expertise in CO to a teleconference to review the scientific content of preliminary draft materials for the draft ISA and the annexes. The purpose of the initial peer review teleconference was to ensure that the ISA is up to date and focused on the most policy-relevant findings, and to assist EPA with integration of evidence within and across disciplines. Subsequently, EPA addressed comments and completed the initial integration and synthesis of the evidence.

The integration of evidence on health or welfare effects involves collaboration between scientists from various disciplines. As described in the section below, the ISA organization is based on health effect categories. As an example, an evaluation of health effects evidence would include summaries of findings from epidemiologic, controlled human exposure, and toxicological studies, and integration of the results to draw conclusions based on the causal framework described below. Using the causal framework described in Section 1.6, EPA scientists consider aspects such as strength, consistency, coherence and biological plausibility of the evidence, and develop draft causality judgments on the nature of the relationships. The draft integrative synthesis sections and conclusions are reviewed by EPA internal experts and, as appropriate, by outside expert authors. In practice, causality determinations often entail an iterative process of review and evaluation of the evidence. The draft ISA is released for review by the CASAC and the public, and comments received on the characterization of the science as well as the implementation of the causal framework are carefully considered in revising and completing the ISA.

1.4. Document Organization

The ISA is composed of five chapters. This introductory chapter presents background information and provides an overview of EPA's framework for making causal judgments. Chapter 2 is an integrated summary of key findings and conclusions regarding the source to dose paradigm, MOA, and important health effects of CO, including cardiovascular, nervous system,

perinatal/developmental, respiratory, and mortality outcomes. Chapter 3 highlights key concepts and evidence relevant to understanding the sources, ambient concentrations, atmospheric behavior, and exposure to ambient CO. Chapter 4 describes the dosimetry and pharmacokinetics of CO, including formation and fate of carboxyhemoglobin (COHb). Chapter 5 presents a discussion of the MOA of CO and evaluates and integrates epidemiologic, human clinical, and animal toxicological information on health effects related to short-term exposures (i.e., hours, days, or weeks) and long-term exposures (i.e., months or years) to CO, including cardiovascular and systemic effects, central nervous system (CNS) effects, birth outcomes and developmental effects, respiratory effects, and mortality.

A series of annexes supplement this ISA. The annexes provide tables summarizing additional details of the pertinent literature published since the last review, as well as selected older studies of particular interest. These annexes contain information on:

- atmospheric chemistry of CO, sampling and analytic methods for measurement of CO concentrations, emissions, sources and human exposure to CO (Annex A);
- studies on the dosimetry and pharmacokinetics of CO (Annex B);
- epidemiologic studies of health effects from short- and long-term exposure to CO (Annex C);
- controlled human exposure studies of health effects related to exposure to CO (Annex D); and
- toxicological studies of health effects in laboratory animals (Annex E)

Within Annexes B through E, detailed information about methods and results of health studies is summarized in tabular format, and generally includes information about concentrations of CO and averaging times, study methods employed, results and comments, and quantitative results for relationships between effects and exposure to CO. As noted in the section above, the most pertinent results of this body of studies are brought into the ISA.

1.5. Document Scope

For the current review of the primary CO standards, relevant scientific information on human exposures and health effects associated with exposure to ambient CO has been assessed. Health effects resulting from accidental exposures to very high concentrations of non-ambient CO (i.e., CO poisoning) are not directly relevant to ambient exposures, and as such, a discussion of these effects has deliberately been excluded from this document. For a detailed review of the effects of high-level exposures to CO, the reader is referred to the extensive body of literature related to CO poisoning (Ernst and Zibrak, 1998, [049822](#); Penney, 2007, [194668](#); Raub et al., 2000, [002180](#)). In addition, results of studies investigating the relationship between blood COHb concentrations and health effects (e.g., Hedblad et al., 2006, [199512](#)) may be informative regarding the biological plausibility of health effects associated with changes in COHb concentrations. However, the lack of data on ambient concentrations and the likely contribution of non-ambient CO to COHb in these studies complicates the interpretation of the results with respect to ambient CO exposure, and therefore these studies will not be discussed in this review. The possible influence of other atmospheric pollutants on the interpretation of the role of CO in health effects studies is considered in this assessment. This includes other pollutants with the potential to co-occur in the environment (e.g., nitrogen dioxide [NO₂], sulfur dioxide [SO₂], ozone [O₃], and particulate matter [PM]).

The review also assesses relevant scientific information associated with known or anticipated public welfare effects that may be identified. The 1979 CO AQCD (U.S. EPA, 1979, [017687](#)) reviewed research on the effects of CO on vegetation and soil microflora, which showed that visible symptoms and effects on growth, yield, and reproduction were observed in some studies at very high CO concentrations (1,000-10,000 ppm or greater), while biochemical and physiological responses, including reduced nitrogen fixation, were observed at lower concentrations (1,000 ppm and below). As discussed in Section 1.3, a critical review of the ecological effects literature identified no

information published since the 1979 CO AQCD (U.S. EPA, 1979, [017687](#)) pertinent to ambient CO exposures; hence, no section on ecological effects appears in this assessment. The reader is referred to the 1979 CO AQCD (U.S. EPA, 1979, [017687](#)) for a detailed discussion of the effects of high CO concentrations on plants and microorganisms. The definition of public welfare for the NAAQS includes considerations of climate. Thus, the climate forcing effects of CO are summarized in Chapter 2 and are discussed in detail in Chapter 3, where distinctions are drawn between global-scale conclusions related to climate and the strongly variable continental and regional climate forcing effects from CO.

1.6. EPA Framework for Causal Determination

The EPA has developed a consistent and transparent basis to evaluate the causal nature of air pollution-induced health or environmental effects. The framework described below establishes uniform language concerning causality and brings more specificity to the findings. This standardized language was drawn from across the federal government and wider scientific community, especially from the recent National Academy of Sciences (NAS) Institute of Medicine (IOM) document, *Improving the Presumptive Disability Decision-Making Process for Veterans*, (2008, [156586](#)) the most recent comprehensive work on evaluating causality.

This introductory section focuses on the evaluation of health effects evidence. While focusing on human health outcomes, the concepts are also generally relevant to causality determination for welfare effects. This section:

- describes the kinds of scientific evidence used in establishing a general causal relationship between exposure and health effects;
- defines cause, in contrast to statistical association;
- discusses the sources of evidence necessary to reach a conclusion about the existence of a causal relationship;
- highlights the issue of multifactorial causation;
- identifies issues and approaches related to uncertainty; and
- provides a framework for classifying and characterizing the weight of evidence in support of a general causal relationship.

Approaches to assessing the separate and combined lines of evidence (e.g., epidemiologic, human clinical, and animal toxicological studies) have been formulated by a number of regulatory and science agencies, including the IOM of the NAS (2008, [156586](#)), International Agency for Research on Cancer (2006, [093206](#)), *EPA Guidelines for Carcinogen Risk Assessment* (2005, [086237](#)), Centers for Disease Control and Prevention (2004, [056384](#)), and National Acid Precipitation Assessment Program (1991, [095894](#)). These formalized approaches offer guidance for assessing causality. The frameworks are similar in nature, although adapted to different purposes, and have proven effective in providing a uniform structure and language for causal determinations. Moreover, these frameworks have supported decision-making under conditions of uncertainty.

1.6.1. Scientific Evidence Used in Establishing Causality

Causality determinations are based on the evaluation and synthesis of evidence from across scientific disciplines; the type of evidence that is most important for such determinations will vary by pollutant or assessment. The most compelling evidence of a causal relationship between pollutant exposures and human health effects comes from human clinical studies. This type of study experimentally evaluates the health effects of administered exposures in human volunteers under highly controlled laboratory conditions.

In epidemiologic or observational studies of humans, the investigator does not control exposures or intervene with the study population. Broadly, observational studies can describe associations between exposures and effects. These studies fall into several categories: cross-sectional, prospective cohort, and time-series studies. “Natural experiments” offer the opportunity to investigate changes in health with a change in exposure; these include comparisons of health effects before and after a change in population exposures, such as closure of a pollution source.

Experimental animal data can help characterize effects of concern, exposure-response relationships, susceptible populations and MOAs. In the absence of controlled human exposure or epidemiologic data, animal data alone may be sufficient to support a likely causal determination, assuming that humans respond similarly to the experimental species.

1.6.2. Association and Causation

“Cause” is a significant, effectual relationship between an agent and an effect on health or public welfare. “Association” is the statistical dependence among events, characteristics, or other variables. An association is *prima facie* evidence for causation; alone, however, it is insufficient proof of a causal relationship between exposure and disease. Unlike an association, a causal claim supports the creation of counterfactual claims; that is, a claim about what the world would have been like under different or changed circumstances (IOM, 2008, [156586](#)). Much of the newly available health information evaluated in this ISA comes from epidemiologic studies that report a statistical association between ambient exposure and health outcome.

Many of the health and environmental outcomes reported in these studies have complex etiologies. Diseases such as asthma, coronary heart disease (CHD) or cancer are typically initiated by multiple agents. Outcomes depend on a variety of factors, such as age, genetic susceptibility, nutritional status, immune competence, and social factors (Gee and Payne-Sturges, 2004, [093070](#); IOM, 2008, [156586](#)). Effects on ecosystems are often also multifactorial with a complex web of causation. Further, exposure to a combination of agents could cause synergistic or antagonistic effects. Thus, the observed risk represents the net effect of many actions and counteractions.

1.6.3. Evaluating Evidence for Inferring Causation

Moving from association to causation involves the elimination of alternative explanations for the association. In estimating the causal influence of an exposure on health or environmental effects, it is recognized that scientific findings incorporate uncertainty. “Uncertainty” can be defined as a state of having limited knowledge where it is impossible to exactly describe an existing state or future outcome, e.g., the lack of knowledge about the correct value for a specific measure or estimate. Uncertainty characterization and uncertainty assessment are two activities that lead to different degrees of sophistication in describing uncertainty. Uncertainty characterization generally involves a qualitative discussion of the thought processes that lead to the selection and rejection of specific data, estimates, scenarios, etc. Uncertainty assessment is more quantitative. The process begins with simpler measures (e.g., ranges) and simpler analytical techniques and progresses, to the extent needed to support the decision for which the assessment is conducted, to more complex measures and techniques. Data will not be available for all aspects of an assessment and those data that are available may be of questionable or unknown quality. In these situations, evaluation of uncertainty can include professional judgment or inferences based on analogy with similar situations. The net result is that the assessment will be based on a number of assumptions with varying degrees of uncertainty. Uncertainties commonly encountered in evaluating health evidence for the criteria air pollutants are outlined below for epidemiologic and experimental studies. Various approaches to evaluating uncertainty include classical statistical methods, sensitivity analysis, or probabilistic uncertainty analysis, in order of increasing complexity and data requirements. The ISA generally evaluates uncertainties qualitatively in assessing the evidence from across studies; in some situations quantitative analysis approaches, such as metaregression, may be used.

Meta-analysis may be a valuable tool for evaluating evidence by combining results from a body of studies. Blair et al. (1995, [079190](#)) observe that meta-analysis can enhance understanding of associations between exposures and effects that are not readily apparent in examination of individual study results and can be particularly useful for formally examining sources of heterogeneity.

However, these authors note that meta-analysis may not be useful when the relationship between the exposure and outcome is obvious, when only a few studies are available for a particular exposure-outcome relationship, where there is limited access to data of sufficient quality, or where there is substantial variation in study design or population. In addition, important differences in effect estimates, exposure metrics, or other factors may limit or even preclude quantitative statistical combination of multiple studies.

Controlled human exposure studies evaluate the effects of exposures to a variety of pollutants in a highly controlled laboratory setting. Also referred to as human clinical studies, these experiments allow investigators to expose subjects to known concentrations of air pollutants under carefully regulated environmental conditions and activity levels. In some instances, controlled human exposure studies can also be used to characterize concentration-response relationships at pollutant concentrations relevant to ambient conditions. Controlled human exposures are typically conducted using a randomized crossover design, with subjects exposed both to CO and a clean air control. In this way, subjects serve as their own controls, effectively controlling for many potential confounders. However, human clinical studies are limited by a number of factors, including a small sample size and short exposure times. The repetitive nature of ambient CO exposures at levels that can vary widely may lead to cumulative health effects, but this type of exposure is not practical to replicate in a laboratory setting. In addition, although subjects do serve as their own controls, personal exposure to pollutants in the hours and days preceding the controlled exposures may vary significantly between and within individuals. Endogenous production of CO creates a body burden of CO that, together with personal exposure from nonambient sources, contributes to baseline COHb levels. Endogenous production rates vary within and among individuals, particularly for individuals with diseases such as hemolytic anemia or chronic inflammation. This body burden of CO and COHb limits the lower range of exposures that can be practically covered in controlled human exposure studies. Finally, human clinical studies require investigators to adhere to stringent health criteria for a subject to be included in the study, and therefore the results cannot necessarily be generalized to an entire population. Although some human clinical studies have included health-compromised individuals such as those with coronary artery disease (CAD), these individuals must also be relatively healthy and do not represent the most sensitive individuals in the population. Thus, a lack of observation of effects from human clinical studies does not necessarily mean that a causal relationship does not exist. While human clinical studies provide important information on the biological plausibility of associations observed between air pollutant exposure and health outcomes in epidemiologic studies, observed effects in these studies may underestimate the response in certain populations.

Epidemiologic studies provide important information on the associations between health effects and exposure of human populations to ambient air pollution. In the evaluation of epidemiologic evidence, one important consideration is potential confounding. Confounding is “. . . a confusion of effects. Specifically, the apparent effect of the exposure of interest is distorted because the effect of an extraneous factor is mistaken for or mixed with the actual exposure effect (which may be null)” (Rothman and Greenland, 1998, [086599](#)). One approach to remove spurious associations due to possible confounders is to control for characteristics that may differ between exposed and unexposed persons; this is frequently termed “adjustment.” Scientific judgment is needed regarding likely sources and magnitude of confounding, together with consideration of how well the existing constellation of study designs, results, and analyses address this potential threat to inferential validity. One key consideration in this review is evaluation of the potential contribution of CO to health effects when it is a component of a complex air pollutant mixture. Reported CO effect estimates in epidemiologic studies may reflect independent CO effects on health outcomes. Ambient CO may also be serving as an indicator of complex ambient air pollution mixtures that share the same source as CO (e.g., motor vehicle emissions). Alternatively, copollutants may mediate the effects of CO or CO may influence the toxicity of copollutants.

Another important consideration in the evaluation of epidemiologic evidence is effect modification. “Effect-measure modification differs from confounding in several ways. The main difference is that, whereas confounding is a bias that the investigator hopes to prevent or remove from the effect estimate, effect-measure modification is a property of the effect under study . . . In epidemiologic analysis one tries to eliminate confounding but one tries to detect and estimate effect-measure modification” (Rothman and Greenland, 1998, [086599](#)). Examples of effect modifiers in some of the studies evaluated in this ISA include environmental variables, such as temperature or humidity, individual risk factors, such as education, cigarette smoking status, age in a prospective

cohort study, and community factors, such as percent of population > 65 yr old. It is often possible to stratify the relationship between health outcome and exposure by one or more of these risk factor variables. For variables that modify the association, effect estimates in each stratum will be different from one another and different from the overall estimate, indicating a different exposure-response relationship may exist in populations represented by these variables. Effect modifiers may be encountered (a) within single-city time-series studies or (b) across cities in a two-stage hierarchical model or meta-analysis.

Several statistical methods are available to detect and control for potential confounders, with none of them being completely satisfactory. Multivariable regression models constitute one tool for estimating the association between exposure and outcome after adjusting for characteristics of participants that might confound the results. The use of multipollutant regression models has been the prevailing approach for controlling potential confounding by copollutants in air pollution health effects studies. Finding the likely causal pollutant from multipollutant regression models is made difficult by the possibility that one or more air pollutants may be acting as a surrogate for an unmeasured or poorly measured pollutant or for a particular mixture of pollutants. In addition, more than one pollutant may exert similar health effects, resulting in independently observed associations for multiple pollutants. For example, PM_{2.5} and NO₂ have each been linked to cardiovascular effects in epidemiologic studies. Correlation between CO concentrations and various copollutants, such as PM_{2.5} and NO₂, makes it difficult to quantitatively interpret associations between different pollutant exposures and health effects. Thus, results of models that attempt to distinguish CO effects from those of copollutants must be interpreted with caution. The number and degree of diversity of covariates, as well as their relevance to the potential confounders, remain matters of scientific judgment. Despite these limitations, the use of multipollutant models is still the prevailing approach employed in most air pollution epidemiologic studies and provides some insight into the potential for confounding or interaction among pollutants.

Another way to adjust for potential confounding is through stratified analysis, i.e., examining the association within homogeneous groups with respect to the confounding variable. The use of stratified analyses has an additional benefit: it allows examination of effect modification through comparison of the effect estimates across different groups. If investigators successfully measured characteristics that distort the results, adjustment of these factors help separate a spurious from a true causal association. Appropriate statistical adjustment for confounders requires identifying and measuring all reasonably expected confounders. Deciding which variables to control for in a statistical analysis of the association between exposure and disease or health outcome depends on knowledge about possible mechanisms and the distributions of these factors in the population under study. Identifying these mechanisms makes it possible to control for potential sources that may result in a spurious association.

Adjustment for potential confounders can be influenced by differential exposure measurement error. There are several components that contribute to exposure measurement error in epidemiologic studies, including the difference between true and measured ambient concentrations, the difference between average personal exposure to ambient pollutants and ambient concentrations at central monitoring sites, and the use of average population exposure rather than individual exposure estimates. Consideration of issues important for evaluation of exposure to ambient CO include: (1) spatial variability of CO concentrations across urban areas, particularly with respect to highly traveled roadways; (2) location of CO monitors at varying distances from roads; and (3) the detection limit of instruments in the CO monitoring network. Previous AQCDs have examined the role of measurement error for non-reactive pollutants in time-series epidemiologic studies using simulated data and mathematical analyses and suggested that transfer of effects from the “causal” variable to the confounder would only occur under unusual circumstances (i.e., “true” predictors having high positive or negative correlation; substantial measurement error; or extremely negatively correlated measurement errors) (U.S. EPA, 2004, [056905](#)).

Confidence that unmeasured confounders are not producing the findings is increased when multiple studies are conducted in various settings using different subjects or exposures, each of which might eliminate another source of confounding from consideration. Thus, multicity studies which use a consistent method to analyze data from across locations with different levels of covariates can provide insight on potential confounding in associations. Intervention studies, because of their quasi-experimental nature, can be particularly useful in characterizing causation.

In addition to clinical and epidemiologic studies, the tools of experimental biology have been valuable for developing insights into human physiology and pathology. Laboratory tools have been

extended to explore the effects of putative toxicants on human health, especially through the study of model systems in other species. These studies evaluate the effects of exposures to a variety of pollutants in a highly controlled laboratory setting and allow exploration of MOAs or mechanisms by which a pollutant may cause effects. Background knowledge of the biological mechanisms by which an exposure might or might not cause disease can prove crucial in establishing or negating a causal claim. Consideration of evidence on the non-hypoxic effects of CO via cell signaling and alteration of heme protein function along with evidence on COHb-mediated hypoxic stress, provides a more complete understanding of the biological response to CO. There are, however, uncertainties associated with quantitative extrapolations between laboratory animals and humans on the pathophysiological effects of any pollutant. Animal species can differ from each other in fundamental aspects of physiology and anatomy (e.g., metabolism, airway branching, hormonal regulation) that may limit extrapolation.

Interpretations of experimental studies of air pollution effects in laboratory animals, as in the case of environmental comparative toxicology studies, are affected by limitations associated with extrapolation models. The differences between humans and rodents with regard to pollutant absorption and distribution profiles based on metabolism, hormonal regulation, breathing pattern, exposure dose, and differences in lung structure and anatomy, all have to be taken into consideration. Also, in spite of a high degree of homology and the existence of a high percentage of orthologous genes across humans and rodents (particularly mice), extrapolation of molecular alterations at the gene level is complicated by species-specific differences in transcriptional regulation. Given these molecular differences, at this time there are uncertainties associated with quantitative extrapolations between laboratory animals and humans of observed pollutant-induced pathophysiological alterations under the control of widely varying biochemical, endocrine, and neuronal factors.

1.6.4. Application of Framework for Causal Determination

EPA uses a two-step approach to evaluate the scientific evidence on health or environmental effects of criteria pollutants. The first step determines the weight of evidence in support of causation and characterizes the strength of any resulting causal classification. The second step includes further evaluation of the quantitative evidence regarding the concentration-response relationships and the loads or levels, duration and pattern of exposures at which effects are observed.

To aid judgment, various “aspects”¹ of causality have been discussed by many philosophers and scientists. The most widely cited aspects of causality in epidemiology, and public health, in general, were articulated by Sir Austin Bradford Hill (1965, [071664](#)) and have been widely used (CDC, 2004, [056384](#); IARC, 2006, [093206](#); IOM, 2008, [156586](#); U.S. EPA, 2005, [086237](#)). These aspects (Hill, 1965, [071664](#)) have been modified (Table 1-2) for use in causal determinations specific to health and welfare effects or pollutant exposures (U.S. EPA, 2009, [179916](#)).² Some aspects are more likely than others to be relevant for evaluating evidence on the health or environmental effects of criteria air pollutants. For example, the analogy aspect does not always apply, especially for the gaseous criteria pollutants, and specificity would not be expected for multi-etiological health outcomes, such as asthma or cardiovascular disease, or ecological effects related to acidification. Aspects that usually play a larger role in determination of causality are consistency of results across studies, coherence of effects observed in different study types or disciplines, biological plausibility, exposure-response relationship, and evidence from “natural” experiments.

¹ The “aspects” described by Hill (1965, [071664](#)) have become, in the subsequent literature, more commonly described as “criteria.” The original term “aspects” is used here to avoid confusion with ‘criteria’ as it is used, with different meaning, in the Clean Air Act.

² The Hill aspects were developed for interpretation of epidemiologic results. They have been modified here for use with a broader array of data, i.e., epidemiologic, controlled human exposure, and animal toxicological studies, as well as in vitro data, and to be more consistent with EPA’s Guidelines for Carcinogen Risk Assessment.

Table 1-1. Aspects to aid in judging causality.

Consistency of the observed association	An inference of causality is strengthened when a pattern of elevated risks is observed across several independent studies. The reproducibility of findings constitutes one of the strongest arguments for causality. If there are discordant results among investigations, possible reasons such as differences in exposure, confounding factors, and the power of the study are considered.
Coherence	An inference of causality from epidemiologic associations may be strengthened by other lines of evidence (e.g., clinical and animal studies) that support a cause-and-effect interpretation of the association. Evidence on ecological or welfare effects may be drawn from a variety of experimental approaches (e.g., greenhouse, laboratory, and field) and subdisciplines of ecology (e.g., community ecology, biogeochemistry and paleological/historical reconstructions). The coherence of evidence from various fields greatly adds to the strength of an inference of causality. The absence of other lines of evidence, however, is not a reason to reject causality.
Biological plausibility.	An inference of causality tends to be strengthened by consistency with data from experimental studies or other sources demonstrating plausible biological mechanisms. A proposed mechanistic linking between an effect and exposure to the agent is an important source of support for causality, especially when data establishing the existence and functioning of those mechanistic links are available. A lack of biologic understanding, however, is not a reason to reject causality.
Biological gradient (exposure-response relationship)	A well characterized exposure-response relationship (e.g., increasing effects associated with greater exposure) strongly suggests cause and effect, especially when such relationships are also observed for duration of exposure (e.g., increasing effects observed following longer exposure times). There are, however, many possible reasons that a study may fail to detect an exposure-response relationship. Thus, although the presence of a biologic gradient may support causality, the absence of an exposure-response relationship does not exclude a causal relationship.
Strength of the observed association	The finding of large, precise risks increases confidence that the association is not likely due to chance, bias, or other factors. However, given a truly causal agent, a small magnitude in the effect could follow from a lower level of exposure, a lower potency, or the prevalence of other agents causing similar effects. While large effects support causality, modest effects therefore do not preclude it.
Experimental evidence.	The strongest evidence for causality can be provided when a change in exposure brings about a change in occurrence or frequency of health or welfare effects.
Temporal relationship of the observed association	Evidence of a temporal sequence between the introduction of an agent, and appearance of the effect, constitutes another argument in favor of causality.
Specificity of the observed association	As originally intended, this refers to increased inference of causality if one cause is associated with a single effect or disease (Hill, 1965, 071664). Based on our current understanding, this is now considered one of the weaker guidelines for causality; for example, many agents cause respiratory disease and respiratory disease has multiple causes. At the scale of ecosystems, as in epidemiology, complexity is such that single agents causing single effects, and single effects following single causes, are extremely unlikely. The ability to demonstrate specificity under certain conditions remains, however, a powerful attribute of experimental studies. Thus, although the presence of specificity may support causality, its absence does not exclude it.
Analogy	Structure activity relationships and information on the agent's structural analogs can provide insight into whether an association is causal. Similarly, information on mode of action for a chemical, as one of many structural analogs, can inform decisions regarding likely causality.

Although these aspects provide a framework for assessing the evidence, they do not lend themselves to being considered in terms of simple formulas or fixed rules of evidence leading to conclusions about causality (Hill, 1965, [071664](#)). For example, one cannot simply count the number of studies reporting statistically significant results or statistically nonsignificant results and reach credible conclusions about the relative weight of the evidence and the likelihood of causality. Rather, these important considerations are taken into account with the goal of producing an objective appraisal of the evidence, informed by peer and public comment and advice, which includes weighing alternative views on controversial issues. In addition, it is important to note that the aspects in Table 1-1 cannot be used as a strict checklist, but rather to determine the weight of the evidence for inferring causality. In particular, not meeting one or more of the principles does not automatically preclude a determination of causality (See discussion in CDC, 2004, [056384](#)).

1.6.5. Determination of Causality

In the ISA, EPA assesses the results of recent relevant publications, building upon evidence available during the previous NAAQS review, to draw conclusions on the causal relationships between relevant pollutant exposures and health or environmental effects. This ISA uses a five-level hierarchy that classifies the weight of evidence for causation, not just association¹; that is, whether the weight of scientific evidence makes causation at least as likely as not, in the judgment of the reviewing group. In developing this hierarchy, EPA has drawn on the work of previous evaluations, most prominently the IOM's *Improving the Presumptive Disability Decision-Making Process for Veterans* (2008, [156586](#)), EPA's Guidelines for Carcinogen Risk Assessment (2005, [086237](#)), and the

¹ It should be noted that the CDC and IOM frameworks use a four-category hierarchy for the strength of the evidence. A five-level hierarchy is used here to be consistent with the EPA Guidelines for Carcinogen Risk Assessment and to provide a more nuanced set of categories.

U.S. Surgeon General’s smoking reports (CDC, 2004, [056384](#)). In the ISA, EPA uses a series of five descriptors to characterize the weight of evidence for causality. This weight of evidence evaluation is based on various lines of evidence from across the health and environmental effects disciplines. These separate judgments are integrated into a qualitative statement about the overall weight of the evidence and causality. The five descriptors for causal determination are described in Table 1-2.

Table 1-2. Weight of evidence for causal determination.

	Health Effects	Ecological and Welfare Effects
Causal relationship	Evidence is sufficient to conclude that there is a causal relationship with relevant pollutant exposures. That is, the pollutant has been shown to result in health effects in studies in which chance, bias, and confounding could be ruled out with reasonable confidence. For example: a) controlled human exposure studies that demonstrate consistent effects; or b) observational studies that cannot be explained by plausible alternatives or are supported by other lines of evidence (e.g., animal studies or mode of action information). Evidence includes replicated and consistent high-quality studies by multiple investigators.	Evidence is sufficient to conclude that there is a causal relationship with relevant pollutant exposures. That is, the pollutant has been shown to result in effects in studies in which chance, bias, and confounding could be ruled out with reasonable confidence. Controlled exposure studies (laboratory or small- to medium-scale field studies) provide the strongest evidence for causality, but the scope of inference may be limited. Generally, determination is based on multiple studies conducted by multiple research groups, and evidence that is considered sufficient to infer a causal relationship is usually obtained from the joint consideration of many lines of evidence that reinforce each other.
Likely to be a causal relationship	Evidence is sufficient to conclude that a causal relationship is likely to exist with relevant pollutant exposures, but important uncertainties remain. That is, the pollutant has been shown to result in health effects in studies in which chance and bias can be ruled out with reasonable confidence but potential issues remain. For example: a) observational studies show an association, but copollutant exposures are difficult to address and/or other lines of evidence (controlled human exposure, animal, or mode of action information) are limited or inconsistent; or b) animal toxicological evidence from multiple studies from different laboratories that demonstrate effects, but limited or no human data are available. Evidence generally includes replicated and high-quality studies by multiple investigators.	Evidence is sufficient to conclude that there is a likely causal association with relevant pollutant exposures. That is, an association has been observed between the pollutant and the outcome in studies in which chance, bias and confounding are minimized, but uncertainties remain. For example, field studies show a relationship, but suspected interacting factors cannot be controlled, and other lines of evidence are limited or inconsistent. Generally, determination is based on multiple studies in multiple research groups.
Suggestive of a causal relationship	Evidence is suggestive of a causal relationship with relevant pollutant exposures, but is limited because chance, bias and confounding cannot be ruled out. For example, at least one high-quality epidemiologic study shows an association with a given health outcome but the results of other studies are inconsistent.	Evidence is suggestive of a causal relationship with relevant pollutant exposures, but chance, bias and confounding cannot be ruled out. For example, at least one high-quality study shows an effect, but the results of other studies are inconsistent.
Inadequate to infer a causal relationship	Evidence is inadequate to determine that a causal relationship exists with relevant pollutant exposures. The available studies are of insufficient quantity, quality, consistency or statistical power to permit a conclusion regarding the presence or absence of an effect.	The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of an effect.
Not likely to be a causal relationship	Evidence is suggestive of no causal relationship with relevant pollutant exposures. Several adequate studies, covering the full range of levels of exposure that human beings are known to encounter and considering susceptible populations, are mutually consistent in not showing an effect at any level of exposure.	Several adequate studies, examining relationships with relevant exposures, are consistent in failing to show an effect at any level of exposure.

For the CO ISA, determination of causality involved the evaluation of evidence for different types of health effects associated with short- and long-term exposure periods. In making determinations of causality for CO, evidence was evaluated for health outcome categories, such as cardiovascular effects, and then conclusions were drawn based upon the integration of evidence from across disciplines (e.g., epidemiology, clinical studies and toxicology) and also across the suite of related individual health outcomes. To accomplish this integration, evidence from multiple and various types of studies was considered. Response was evaluated over a range of observations which was determined by the type of study and methods of exposure or dose and response measurements. Results from different protocols were compared and contrasted.

In drawing judgments regarding causality for the criteria air pollutants, EPA focuses on evidence of effects at relevant pollutant exposures. To best inform reviews of the NAAQS, these evaluations go beyond a determination of causality at any dose or concentration to emphasize the relationship apparent at relevant pollutant exposures. Concentrations generally within an order of magnitude or two of ambient pollutant measurements are considered to be relevant for this determination. Building upon the determination of causality are questions relevant to quantifying health or environmental risks based on our understanding of the quantitative relationships between pollutant exposures and health or welfare effects. While the causality determination is based primarily on evaluation of health or environmental effects evidence, EPA also evaluates evidence related to the doses or levels at which effects are observed. Considerations relevant to evaluation of quantitative relationships for health and environmental effects are summarized below.

1.6.5.1. Effects on Human Populations

Once a determination is made regarding the causal relationship between the pollutant and outcome category, important questions regarding quantitative relationships include:

- What is the concentration-response, exposure-response, or dose-response relationship in the human population?
- What is the interrelationship between incidence and severity of effect?
- What exposure conditions (dose or exposure, duration and pattern) are important?
- What populations appear to be differentially affected (i.e., more susceptible to effects)?

To address these questions, the entirety of policy-relevant quantitative evidence is evaluated to best quantify those concentration-response relationships that exist. This requires evaluation of pollutant concentrations and exposure durations at which effects were observed for exposed populations, including potentially susceptible populations. This integration of evidence resulted in identification of a study or set of studies that best approximated the concentration-response relationships between health outcomes and CO, given the current state of knowledge and the uncertainties that surrounded these estimates. To accomplish this, evidence is considered from multiple and diverse types of studies. To the extent available, the ISA evaluates results from across epidemiologic studies that use various methods to evaluate the form of relationships between CO and health outcomes and draws conclusions on the most well-supported shape of these relationships. Animal data may also inform evaluation of concentration-response relationships, particularly relative to MOAs and characteristics of susceptible populations. Chapter 2 presents the integrated findings informative for evaluation of population risks.

An important consideration in characterizing the public health impacts associated with exposure to a pollutant is whether the concentration-response relationship is linear across the full concentration range encountered or if nonlinear relationships exist along any part of this range. Of particular interest is the shape of the concentration-response curve at and below the level of the current standards. The shape of the concentration-response curve varies, depending on the type of health outcome, underlying biological mechanisms and dose. At the human population level, however, various sources of variability and uncertainty, such as the low data density in the lower concentration range, possible influence of exposure measurement error, and individual differences in susceptibility to air pollution health effects, tend to smooth and “linearize” the concentration-response function. In addition, many chemicals and agents may act by perturbing naturally occurring background processes that lead to disease, which also linearizes population concentration-response relationships (Clewell and Crump, 2005, [156359](#); Crump et al., 1976, [003192](#); Hoel, 1980, [156555](#)). These attributes of population dose-response may explain why the available human data at ambient concentrations for some environmental pollutants (e.g., PM, O₃, lead [Pb], environmental tobacco smoke [ETS], radiation) do not exhibit evident thresholds for cancer or noncancer health effects, even though likely mechanisms include nonlinear processes for some key events. These attributes of human population dose-response relationships have been extensively discussed in the broader epidemiologic literature (Rothman and Greenland, 1998, [086599](#)).

Publication bias is a source of uncertainty regarding the magnitude of health risk estimates. It is well understood that studies reporting non-null findings are more likely to be published than reports of null findings, and publication bias can also result in overestimation of effect estimate sizes (Ioannidis, 2008, [188317](#)). For example, effect estimates from single-city epidemiologic studies have been found to be generally larger than those from multicity studies (Anderson et al., 2005, [087916](#)). Although publication bias commonly exists for many research areas, it may be present to a lesser degree for epidemiologic studies on CO. In general, epidemiologic studies have focused on the effects of PM, and CO was largely considered as a potentially confounding copollutant of PM. Thus, CO effect estimates may have been presented in these studies regardless of the statistical significance of the results.

Finally, identification of the susceptible population groups contributes to an understanding of the public health impact of pollutant exposures. In this ISA, the term “susceptible population” will be used as an overarching concept to encompass populations variously described as susceptible,

vulnerable, or sensitive. “Susceptible populations” is defined here as those populations that have a greater likelihood of experiencing health effects related to exposure to an air pollutant (e.g., CO) due to a variety of factors including but not limited to: genetic or developmental factors, race, gender, lifestage, lifestyle (e.g., smoking status and nutrition) or preexisting disease; as well as population-level factors that can increase an individual's exposure to an air pollutant (e.g., CO) such as socioeconomic status [SES], which encompasses reduced access to health care, low educational attainment, residential location, and other factors. Epidemiologic studies can help identify susceptible populations by evaluating health responses in the study population. Examples include stratified analyses for subsets of the population under study or testing for interactions or effect modification by factors such as gender, age group, or health status. Experimental studies using animal models of susceptibility or disease can also inform the extent to which health risks are likely greater in specific population groups. Further discussion of these groups is presented in Section 5.7.

1.6.5.2. Effects on Ecosystems or Public Welfare

Key questions for understanding the quantitative relationships between exposure (or concentration or deposition) to a pollutant and risk to ecosystems or the public welfare include:

- What elements of the ecosystem (e.g., types, regions, taxonomic groups, populations, functions, etc.) appear to be affected, or are more sensitive to effects?
- Under what exposure conditions (amount deposited or concentration, duration and pattern) are effects seen?
- What is the shape of the concentration-response or exposure-response relationship?

Evaluations of causality generally consider the probability of quantitative changes in ecological and welfare effects in response to exposure. A challenge to the quantification of exposure-response relationships for ecological effects is the great regional and local variability in ecosystems. Thus, exposure-response relationships are often determined for a specific ecological system and scale, rather than at the national or even regional scale. Quantitative relationships therefore are available site by site. For example, an ecological response to deposition of a given pollutant can differ greatly between ecosystems. Where results from greenhouse or animal ecotoxicological studies are available, they may be used to aid in characterizing exposure-response relations, particularly relative to mechanisms of action, and characteristics of sensitive biota.

1.6.6. Concepts in Evaluating Adversity of Health Effects

In evaluating the health evidence, a number of factors can be considered in determining the extent to which health effects are “adverse” for health outcomes such as changes in lung function or in cardiovascular health measures. Some health outcome events, such as hospitalization for respiratory or cardiovascular diseases, are clearly considered adverse; what is more difficult is determining the extent of change in the more subtle health measures that is adverse. What constitutes an adverse health effect may vary between populations. Some changes in healthy individuals may not be considered adverse while those of a similar type and magnitude are potentially adverse in more susceptible individuals.

For example, the extent to which changes in lung function are adverse has been discussed by the American Thoracic Society (ATS) in an official statement titled *What Constitutes an Adverse Health Effect of Air Pollution?* (2000, [011738](#)). This statement updated the guidance for defining adverse respiratory health effects that had been published 15 years earlier (ATS, 1985, [006522](#)), taking into account new investigative approaches used to identify the effects of air pollution and reflecting concern for impacts of air pollution on specific susceptible groups. In the 2000 update, there was an increased focus on quality of life measures as indicators of adversity and a more specific consideration of population risk. Exposure to air pollution that increases the risk of an adverse effect to the entire population is viewed as adverse, even though it may not increase the risk of any identifiable individual to an unacceptable level. For example, a population of asthmatics could have a distribution of lung function such that no identifiable individual has a level associated with significant impairment. Exposure to air pollution could shift the distribution such that no

identifiable individual experiences clinically relevant effects. This shift toward decreased lung function, however, would be considered adverse because individuals within the population would have diminished reserve function and therefore would be at increased risk to further environmental insult.

It is important to recognize that the more subtle health outcomes may be linked to health events that are clearly adverse. For example, air pollution has been shown to affect markers of transient myocardial ischemia such as ST-segment abnormalities and onset of exertional angina. In some cases, these effects are silent yet may still increase the risk of a number of cardiac events, including MI and sudden death.

1.7. Summary

This ISA is a concise evaluation and synthesis of the most policy-relevant science for reviewing the NAAQS for CO, and it is the chief means for communicating the critical science judgments relevant to that NAAQS review. It reviews the most policy-relevant evidence from atmospheric science, exposure, and health and environmental effects studies and includes mechanistic evidence from basic biological science. This final ISA incorporates clarification and revisions based on public comments and advice and comments provided by EPA's CASAC on the first and second draft ISAs (Brain and Samet, 2009, [194669](#); Brain and Samet, 2010, [202840](#)). Annexes to the ISA provide additional details of the literature published since the last review. A framework for making critical judgments concerning causality was presented in this chapter. It relies on a widely accepted set of principles and standardized language to express evaluation of the evidence. This approach can bring rigor and clarity to current and future assessments. This ISA should assist EPA and others, now and in the future, to accurately represent what is presently known and what remains unknown concerning the effects of CO on human health and public welfare.

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Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at <http://epa.gov/hero>. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISAs) and the Integrated Risk Information System (IRIS).

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