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United States Environmental Protection Agency

Integrated Science Assessment for Ozone and Related Photochemical Oxidants

April 2020

Center for Public Health and Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Research Triangle Park, NC

EXECUTIVE SUMMARY

ES.1 Purpose and Scope of the Integrated Science Assessment

This Integrated Science Assessment (ISA)[1] is a comprehensive evaluation and synthesis of the policy-relevant science aimed at characterizing the health and welfare[2] effects caused by ozone. It communicates critical science judgments of the health-based and welfare-based criteria for ozone and related photochemical oxidants in ambient air. In 2015, the U.S. EPA lowered the health- and welfare-based National Ambient Air Quality Standards (NAAQS) for ozone to 0.070 ppm (annual fourth-highest daily max 8-hour concentration averaged over 3 years[3]). The health-based ozone NAAQS is meant to protect public health, including at-risk populations such as children and people with asthma, with an adequate margin of safety. The welfare-based ozone standard is intended to protect the public welfare from known or anticipated adverse effects associated with the presence of ozone in ambient air.

The ISA identifies and critically evaluates the most policy-relevant scientific literature across scientific disciplines, including epidemiology, controlled human exposure studies, animal toxicology, atmospheric science, exposure science, vegetation studies, agricultural science, ecology, and climate-related science. Key scientific conclusions (e.g., causality determinations; Section ES.4) are presented and explained. These conclusions provide the scientific basis for developing risk and exposure analyses, policy evaluations, and policy decisions for the review. This ISA draws conclusions about the causal nature of the relationships between ozone exposure and health and welfare effects by integrating recent evidence across scientific disciplines with the evidence base evaluated in previous reviews. U.S. EPA engages the Clean Air Scientific Advisory Committee (CASAC) as an independent federal advisory committee to conduct peer reviews of draft ISA and other materials. Peer review comments provided by the CASAC and public comments about the external review draft were considered in the development of this ISA (Section 10.4). The ISA thus provides the policy-relevant scientific information necessary to conduct a review of the NAAQS.

This Executive Summary provides an overview of the important conclusions drawn in the ISA across scientific disciplines, beginning with information on sources, concentrations, estimated background concentrations of ozone and ozone exposure, followed by health and welfare effects. A more detailed summary of the evidence is presented in the Integrated Synthesis, and individual Appendices for

[1] The general process for developing an ISA, including the framework for evaluating weight of evidence and drawing scientific conclusions and causality determinations, is described in a companion document, Preamble to the Integrated Science Assessments (U.S. EPA, 2015), www.epa.gov/isa.

[2] Under Clean Air Act section 302(h), effects on welfare include, but are not limited to, "effects on soils, water, crops, vegetation, manmade 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."

[3] Final rule signed October 1, 2015, and effective December 28, 2015 (80 FR 65291).

each topic area include study-level information and an in-depth characterization of the weight-of-evidence conclusions.

ES.2 Ozone in Ambient Air

The general photochemistry of tropospheric ozone is well-established. Ozone is produced in urban areas and downwind of sources mainly by the reaction of volatile organic compounds (VOCs) with oxides of nitrogen (NO_X) in the presence of sunlight, and outside of polluted areas mainly by reactions of carbon monoxide (CO) and methane (CH_4) with NO_X (Section 1.4). Recent developments in understanding ozone chemistry include observations of higher ozone concentrations during the winter in some western U.S. mountain basins (Section 1.4.1) and new research on the role of marine halogen chemistry in suppressing coastal ozone concentrations (Section 1.4.2). Air monitoring data for the period 2015−2017 show that U.S. daily max 8-hour avg concentrations of ozone (MDA8) are higher in spring and summer (median = 46 ppb) than in autumn (median = 38 ppb) and winter (median = 34 ppb). Figure ES-1 shows the highest values of the 3-year avg of annual fourth-highest MDA8 ozone concentrations (design values above 70 ppb) occur in central and southern California, Arizona, Colorado, Utah, Texas, along the shore of Lake Michigan, and in the Northeast Corridor, typically during the ozone season between May and September (Section 1.2.1.1).

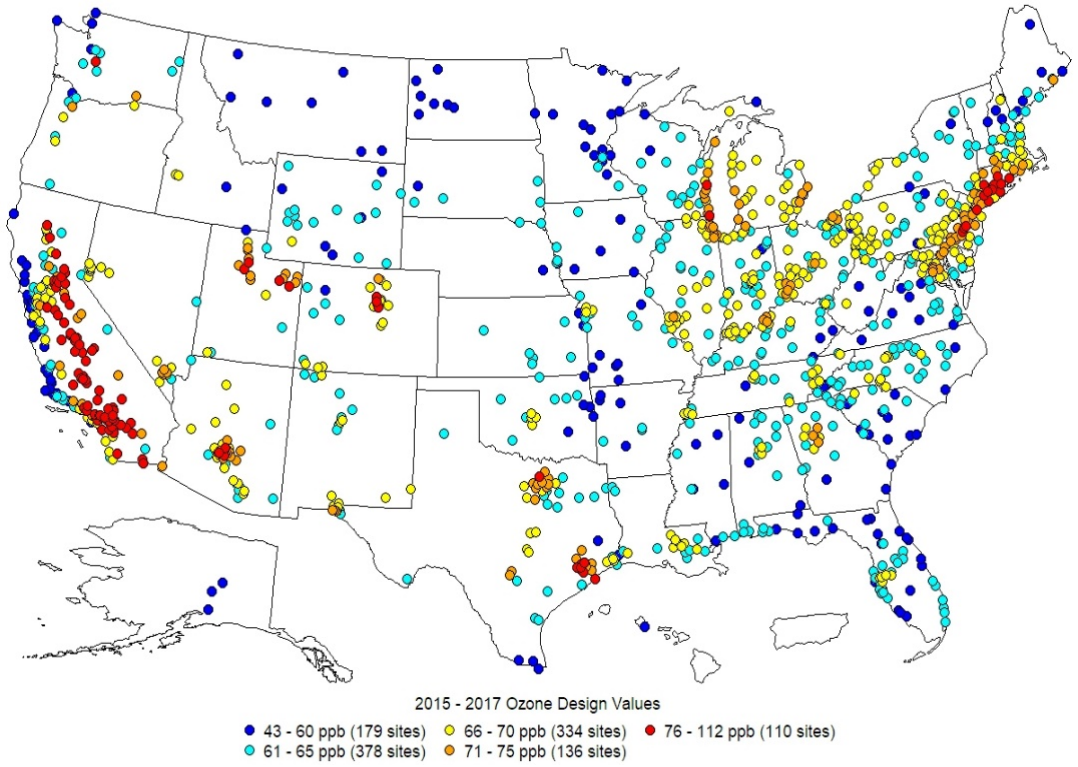


Figure ES-1 Individual monitor ozone concentrations in terms of design values (i.e., 3-year avg of annual fourth-highest max daily 8-hour avg ozone concentration) for 2015−2017.

A better understanding of the origins of ground-level U.S. background (USB) ozone and its concentration trends has emerged since the 2013 Ozone ISA. USB ozone concentration is defined as the ozone concentration that would occur if all U.S. anthropogenic ozone precursor emissions were removed (Section IS.2.2). Major contributors to USB ozone concentrations are stratospheric exchange, international transport, wildfires, lightning, global methane emissions, and natural biogenic and geogenic precursor emissions. Ozone monitors cannot discern the portion of ambient ozone concentrations that come from USB. Instead, USB concentrations are estimated using photochemistry and transport models. The estimates of USB ozone concentrations include uncertainties of about 10 ppb for seasonal average concentrations, with higher uncertainty for MDA8 concentrations. Models consistently estimate higher USB ozone concentrations at higher elevations of the western U.S. than in the eastern U.S. or along the Pacific coast. The estimated seasonal pattern in USB ozone concentrations tends to indicate lower USB in the summer than during the rest of the year. Several modeling studies using different approaches indicate that for MDA8 concentrations above 50−60 ppb, USB concentration estimates generally do not increase with increasing total ozone concentration (i.e., USB ozone concentrations are no higher on high ozone days than on low or moderate ozone days). The temporal trend in estimated USB ozone concentrations indicates increasing concentrations at high elevation western U.S. sites through approximately 2010.

Recently, however, this trend has shown signs of slowing or even reversing, possibly due to decreasing East Asian precursor emissions.

ES.3 Exposure to Ozone

Ambient air ozone concentrations, either measured at fixed-site monitors or estimated by models, are often used as surrogates for personal exposure in epidemiologic studies. Exposure measurement error can lead to reduced precision and an underestimation of the association between short-term ambient ozone exposure and a health effect (Section 2.6.1). For studies of long-term exposure, the true effect of exposure to ambient ozone may be underestimated or overestimated when the exposure model respectively overestimates or underestimates ozone exposure. It is much more common for the effect to be underestimated, and bias in the effect estimate is typically small in magnitude (Section 2.6.2). The availability and sophistication of models to predict ambient ozone concentrations to estimate exposure have increased substantially in recent years (Section 2.3.2). For effects elicited by ozone, the use of exposure estimates that do not account for population behavior and mobility (e.g., via use of time-activity data) may result in underestimation of the true effect and reduced precision (Section 2.4.1).

Tropospheric ozone can cause plant damage, which can then have negative impacts on terrestrial ecosystems as shown in observational and controlled exposure studies and in models using experimental data to extrapolate to effects at the community and ecosystem scale. Robust exposure indices that quantify exposure as it relates to measured plant response (e.g., growth) have been in use for decades and are derived from hourly ozone concentrations. Exposure duration influences the degree of plant response, and ozone effects on plants are cumulative. Cumulative indices summarize ozone concentrations over time and provide a consistent metric for reviewing and comparing exposure-response effects obtained from various studies. Cumulative indices of exposure that differentially weight hourly concentrations have been found to be best suited to characterize vegetation exposure to ozone with regard to reductions in vegetation growth and yield (Section 8.1.2.1).

ES.4 Health and Welfare Effects of Ozone Exposure

Broad health and welfare effect categories are evaluated independently in the Appendices of this ISA. Determinations are made about causation by evaluating evidence across scientific disciplines and are based on judgments of consistency, coherence, and biological plausibility of observed effects, as well as related uncertainties. The ISA uses a formal causality framework to classify the weight of evidence using a five-level hierarchy described in Table II of the Preamble (U.S. EPA, 2015). The subsequent sections characterize the evidence that forms the basis of causality determinations for health and welfare effect categories of a "causal relationship" or a "likely to be causal relationship," or describe instances where a causality determination has changed (i.e., "likely to be causal" changed to "suggestive of, but not sufficient to infer, a causal relationship"). Other relationships between ozone and health effects are *"suggestive of, but not sufficient to infer*" and "*inadequate to infer*" a causal relationship. These causality

determinations appear in Table ES-1, and are more fully discussed in the respective health effects Appendices.

ES.4.1 Health Effects of Ozone Exposure

Ozone-induced effects can occur through a variety of complex pathways within the body. After inhalation, ozone reacts with lipids, proteins, and antioxidants in the epithelial lining fluid of the respiratory tract, creating secondary oxidation products (Section 5.2.3). Initial ozone exposure leads to physiological reactions that may induce a host of autonomic, endocrine, immune, and inflammatory responses throughout the body at the cellular, tissue, and organ level. Recent evidence continues to support ozone-induced effects on the respiratory system. In addition, recent evidence indicates that short-term exposure to ozone is likely to induce metabolic effects, as shown in Figure ES-2. There is also some evidence that ozone exposure can affect the cardiovascular and nervous systems, reproduction and development, and mortality, although there are more uncertainties associated with interpretation of the evidence for these effects.

Table ES-1 Summary of causality determinations by exposure duration and health outcome.

Health Outcome[a]	Conclusions from 2013 Ozone ISA	Conclusions in the 2020 ISA
Short-term exposure to ozone		
Respiratory effects	Causal relationship	Causal relationship
Cardiovascular effects	Likely to be causal relationship	Suggestive of, but not sufficient to infer, a causal relationship[c]
Metabolic effects	No determination made	Likely to be causal relationship[b]
Total mortality	Likely to be causal relationship	Suggestive of, but not sufficient to infer, a causal relationship[c]
Central nervous system effects	Suggestive of a causal relationship[d]	Suggestive of, but not sufficient to infer, a causal relationship
Long-term exposure to ozone		
Respiratory effects	Likely to be causal relationship	Likely to be causal relationship
Cardiovascular effects	Suggestive of a causal relationship[d]	Suggestive of, but not sufficient to infer, a causal relationship
Metabolic effects	No determination made	Suggestive of, but not sufficient to infer, a causal relationship[b]
Total mortality	Suggestive of a causal relationship[d]	Suggestive of, but not sufficient to infer, a causal relationship
Reproductive effects	Suggestive of a causal relationship[d]	Effects on fertility and reproduction: suggestive of, but not sufficient to infer, a causal relationship[b]
		Effects on pregnancy and birth outcomes: suggestive of, but not sufficient to infer, a causal relationship[b]
Central nervous system effects	Suggestive of a causal relationship[d]	Suggestive of, but not sufficient to infer, a causal relationship
Cancer	Inadequate to infer a causal relationship	Inadequate to infer the presence or absence of a causal relationship[e]

[a]Health effects (e.g., respiratory effects, cardiovascular effects) include the spectrum of outcomes, from measurable subclinical effects (e.g., decrements in lung function, blood pressure) to observable effects (e.g., medication use, hospital admissions) and cause-specific mortality. Total mortality includes all-cause (nonaccidental) mortality, as well as cause-specific mortality.

[b]Denotes new causality determination.

[c]Denotes change in causality determination from 2013 Ozone ISA.

[d]Since the 2013 Ozone ISA, the causality determination language has been updated and this category is now stated as suggestive of, but not sufficient to infer, a causal relationship.

[e]Since the 2013 Ozone ISA, the causality determination language has been updated and this category is now stated as inadequate to infer the presence or absence of a causal relationship.

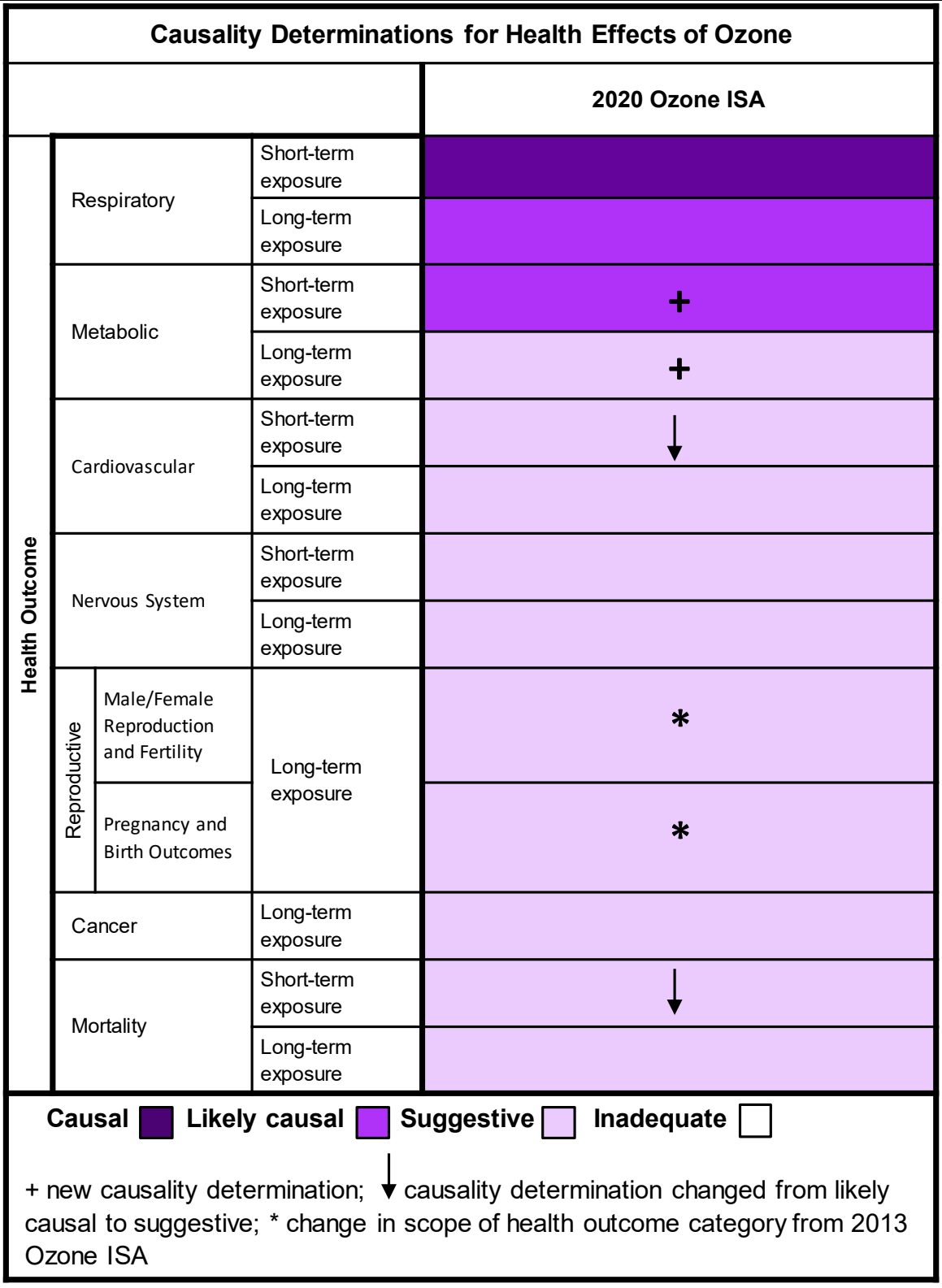


Figure ES-2 Causality determinations for health effects of short- and long-term exposure to ozone.

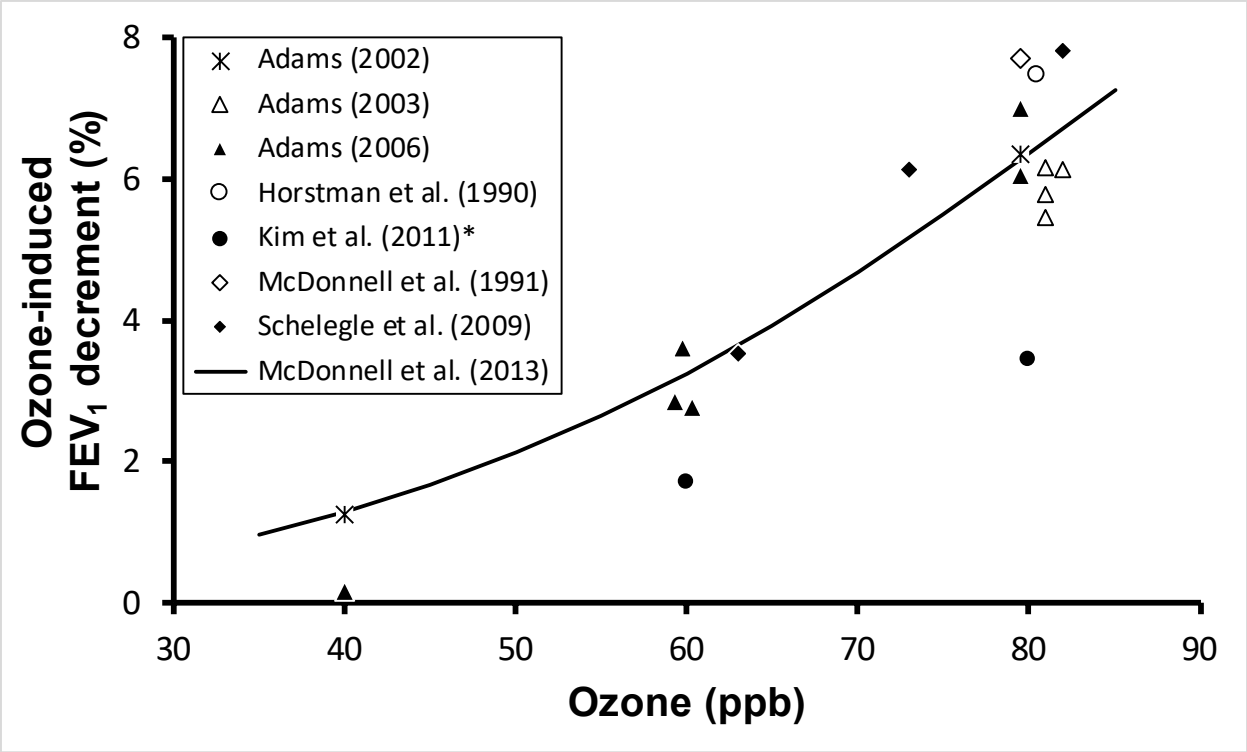
The strongest evidence for health effects due to ozone exposure continues to come from studies of short- and long-term ozone exposure and respiratory health, and this evidence is detailed in Appendix 3. Consistent with conclusions from the 2013 Ozone ISA (Table ES-1), **there is a "causal relationship" between short-term ozone exposure and respiratory effects** (Section 3.1.11), and **there is a "likely to be causal relationship" between long-term ozone exposure and respiratory effects** (Section 3.2.6).

For short-term ozone exposure, controlled human exposure studies conducted over many decades provide experimental evidence for ozone-induced lung function decrements (Figure ES-3), airway responsiveness, respiratory symptoms, and respiratory tract inflammation. Epidemiologic studies continue to provide evidence that ozone concentrations in ambient air are associated with a range of respiratory effects, including asthma exacerbation, chronic obstructive pulmonary disease (COPD) exacerbation, respiratory infection, and hospital admissions and emergency department (ED) visits for combined respiratory diseases.

A large body of animal toxicological studies demonstrate ozone-induced alterations in lung function, inflammation, increased airway responsiveness, and impaired lung host defense. These animal toxicological studies also aid in our understanding of potential mechanisms underlying respiratory effects at the population level and the biological plausibility of epidemiologic associations between short-term ozone exposure and respiratory-related ED visits and hospital admissions.

With respect to long-term ozone exposure, there is strong coherence between animal toxicological studies of changes in lung morphology and epidemiologic studies reporting positive associations between long-term ozone exposure and new-onset asthma, respiratory symptoms in children with asthma, and respiratory mortality. Furthermore, the experimental evidence provides biologically plausible pathways through which long-term ozone exposure could lead to respiratory effects reported in epidemiologic studies.

Metabolic effects related to ozone exposure are evaluated as a separate health endpoint category for the first time in this ISA (Appendix 5). Recent evidence from animal toxicological, controlled human exposure, and epidemiologic studies indicate that **there is a "likely to be causal relationship" between short-term ozone exposure and metabolic effects** (Section 5.1.8). The strongest evidence for this determination is provided by animal toxicological studies that demonstrate impaired glucose tolerance, increased serum triglycerides, fasting hyperglycemia, and increased hepatic gluconeogenesis in various stocks/strains of animals across multiple laboratories. Biological plausibility is provided by results from controlled human exposure and animal toxicological studies that demonstrate activation of sensory nerve pathways following ozone exposure triggers the central neuroendocrine stress response, which includes increased corticosterone, cortisol, and epinephrine production. These findings are coherent with epidemiologic studies that report associations between ozone exposure and perturbations in glucose and insulin homeostasis. In addition, these pathophysiological changes are often accompanied by increased inflammatory markers in peripheral tissues and by activation of the neuroendocrine system.



All responses at and above 70 ppb (targeted concentration) were statistically significant ($p < 0.05$). Adams (2006) found statistically significant responses to square-wave chamber exposures at 60 ppb based on the analysis of Brown et al. (2008) and Kim et al. (2011). During each hour of the exposures, subjects were engaged in moderate quasi-continuous exercise (20 L/minute per m^2 BSA) for 50 minutes and rest for 10 minutes. Following the 3rd hour, subjects had an additional 35-minute rest period for lunch. The data at 60 and 80 ppb have been offset on the *x* axis for illustrative purposes. The solid line illustrates the predicted FEV_1 decrements using Model 3 coefficients at 6.6 hours as a function of ozone concentration for a 23.8-year-old with a BMI of 23.1 kg/m^2 from McDonnell et al. (2013).

*80 ppb data for 30 health subjects were collected as part of the Kim et al. (2011) study, but only published in Figure 5 of McDonnell et al. (2012).

Adapted from Figure 6-1 of 2013 Ozone ISA (U.S. EPA, 2013). Studies appearing in the figure legend are: Adams (2006), Adams (2003), Adams (2002), Horstman et al. (1990), Kim et al. (2011), McDonnell et al. (2013), McDonnell et al. (1991), and Schelegle et al. (2009).

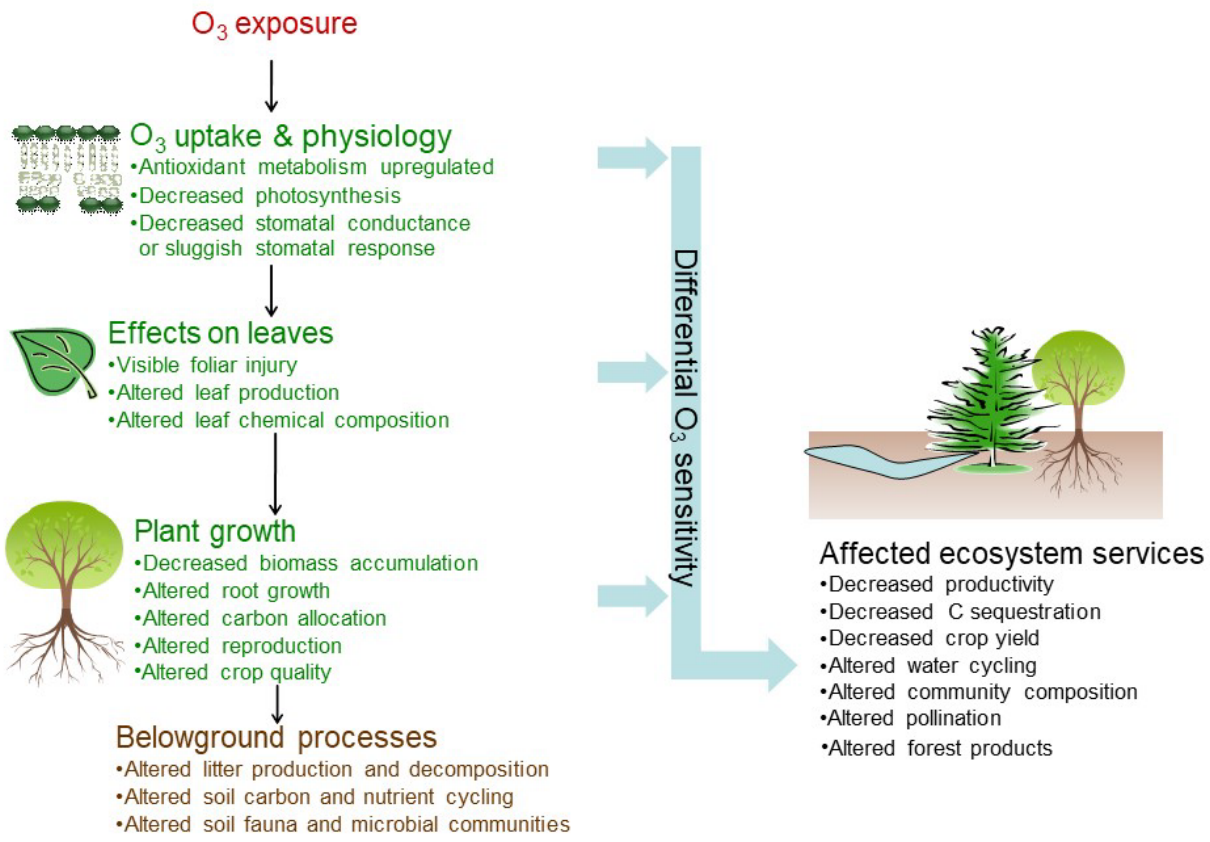
Figure ES-3 Cross-study comparisons of mean decrements in ozone-induced forced expiratory volume in 1 second (FEV_1) in young, healthy adults following 6.6 hours of exposure to ozone.

Notably, there are changes in the causality determinations for short-term ozone exposure and cardiovascular effects (Appendix 4), as well as for total mortality (Appendix 6). In both instances, the evidence synthesized in the 2013 Ozone ISA was sufficient to conclude a "likely to be causal relationship," but after integrating the previous evidence with recent data, **the collective evidence is "suggestive of, but not sufficient to infer, a causal relationship" between short-term ozone exposure and cardiovascular effects (Section 4.1.17) or total mortality (Section 6.1.8)** in this ISA. The evidence that supports this change in the causality determinations includes: (1) a growing body of controlled human exposure studies providing less consistent evidence for an effect of short-term ozone exposure on

cardiovascular health endpoints; (2) a paucity of positive evidence from epidemiologic studies for more severe cardiovascular morbidity endpoints (i.e., heart failure, ischemic heart disease and myocardial infarction, arrhythmia and cardiac arrest, and stroke); and (3) uncertainties due to a lack of control for potential confounding by copollutants in epidemiologic studies. Although there is generally consistent evidence for a limited number of ozone-induced cardiovascular endpoints in animal toxicological studies and for cardiovascular mortality in epidemiologic studies, these results are not coherent with results from controlled human exposure and epidemiologic studies examining cardiovascular morbidity endpoints. There remains evidence for ozone-induced cardiovascular mortality from epidemiologic studies. However, inconsistent results from a larger number of recent controlled human exposure studies that do not provide evidence of cardiovascular effects in response to short-term ozone exposure introduce additional uncertainties.

ES.4.2 Ozone Exposure and Welfare Effects

The scientific evidence for welfare effects of ozone consists mainly of effects on vegetation and ecosystems (Appendix 8) and effects on climate (Appendix 9). For ecological effects, damage to terrestrial ecosystems as evaluated through controlled exposure studies, observational studies and modeling based on experimental data, is largely a function of uptake of ozone into the leaf via stomata (gas exchange openings on leaves). Subsequent reactions with plant tissues alter whole-plant responses that cascade up to effects at higher levels of biological organization (i.e., from the cellular and subcellular level to the individual organism up to ecosystem level processes and services; Figure ES-4). At the leaf level, ozone uptake produces reactive oxygen species that affect cellular function (Section 8.1.3 and Figure 8-2). Reduced photosynthesis, altered carbon allocation, and impaired stomatal function lead to observable responses in plants. Observed vegetation responses to ozone include visible foliar injury (Section IS.5.1.1), and whole-plant level responses (Section IS.5.1.2), which encompass reduction in aboveground and belowground growth, reproduction and yield. Plant-fauna linkages affected by ozone include herbivores that feed on ozone-damaged vegetation and interactions of ozone with compounds emitted by plants that can alter attraction of pollinators to plants (Section IS.5.1.3). A combination of observational and experimental data, and modeling output provides evidence for broad changes in ecosystems such as decreased productivity and carbon sequestration (Section IS.5.1.4), altered belowground processes (Section IS.5.1.5), terrestrial community composition (Section IS.5.1.6), and water cycling (Section IS.5.1.7).



Source: Adapted from U.S. EPA (2013).

Figure ES-4 Illustrative diagram of ozone effects cascading from the cellular level to plants and ecosystems.

There are 12 causality determinations for ecological effects of ozone generally organized from the individual-organism scale to the ecosystem scale in Figure ES-5. Like the findings of the 2013 Ozone ISA (Table ES-2), five are causal relationships (i.e., visible foliar injury, reduced vegetation growth, reduced crop yield, reduced productivity, and altered belowground biogeochemical cycles) and two are likely to be causal relationships (i.e., reduced carbon sequestration, altered ecosystem water cycling). One of the endpoints, alteration of terrestrial community composition, is now concluded to be a causal relationship whereas in the 2013 Ozone ISA this endpoint was classified as a likely to be causal relationship. Three new endpoint categories (i.e., increased tree mortality, alteration of herbivore growth and reproduction, alteration of plant-insect signaling) not evaluated in the 2013 Ozone ISA, are all determined to have a likely to be causal relationship with ozone. Plant reproduction, previously considered as part of the evidence for growth effects, is now a stand-alone causal relationship.

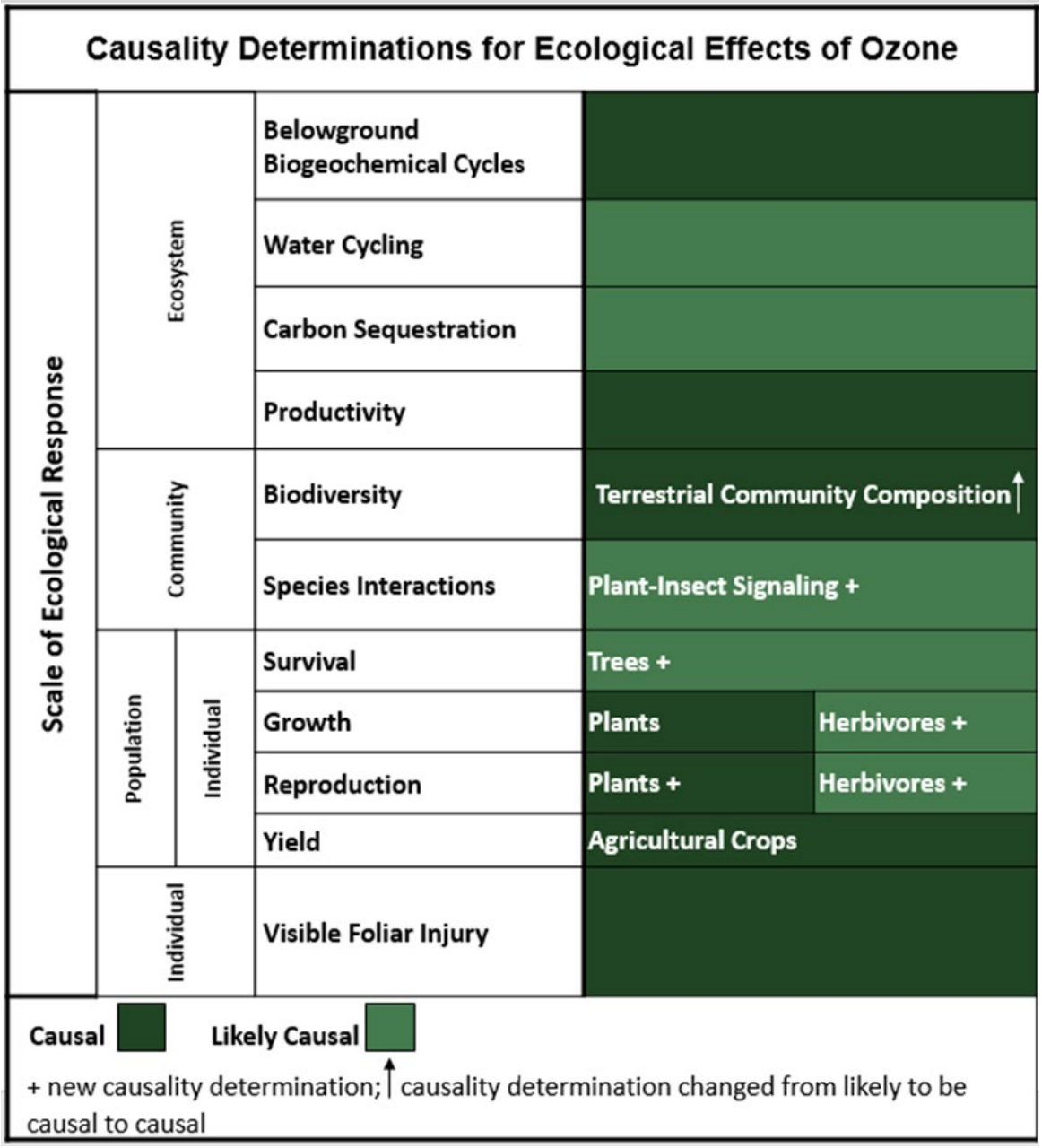


Figure ES-5 Causality determinations for ozone across biological scales of organization and taxonomic groups.

Table ES-2 Summary of causality determinations for ecological effects.

Endpoint	Conclusions from 2013 Ozone ISA	Conclusions in the 2020 ISA
Visible foliar injury	Causal relationship	Causal relationship
Reduced vegetation growth	Causal relationship	Causal relationship
Reduced plant reproduction	No separate causality determination; included with plant growth	Causal relationship[a]
Increased tree mortality	Causality not assessed	Likely to be causal relationship[a]
Reduced yield and quality of agricultural crops	Causal relationship	Causal relationship
Alteration of herbivore growth and reproduction	Causality not assessed	Likely to be causal relationship[a]
Alteration of plant-insect signaling	Causality not assessed	Likely to be causal relationship[a]
Reduced productivity in terrestrial ecosystems	Causal relationship	Causal relationship
Reduced carbon sequestration in terrestrial ecosystems	Likely to be causal relationship	Likely to be causal relationship
Alteration of belowground biogeochemical cycles	Causal relationship	Causal relationship
Alteration of terrestrial community composition	Likely to be causal relationship	Causal relationship[b]
Alteration of ecosystem water cycling	Likely to be causal relationship	Likely to be causal relationship

[a]Denotes new causality determination.

[b]Denotes change in causality determination from 2013 Ozone ISA.

Visible foliar injury resulting from exposure to ozone has been well characterized and documented in over six decades of controlled experimental research involving many tree, shrub, herbaceous, and crop species and using both long-term field studies and laboratory approaches. Recent experimental evidence (Section 8.2) continues to show a consistent association between visible injury and ozone exposure supporting the conclusion of the 2013 Ozone ISA that, **there is a "causal relationship" between ozone and visible foliar injury.** Measured changes in photosynthesis and carbon allocation in ozone-exposed plants scale up to reduced growth documented in natural and managed (e.g., agriculture, forestry, landscaping) species (Section 8.3), as well as impaired reproduction in individual plants (Section 8.4.1). Consistent with the conclusions in the 2013 Ozone ISA, there is **a "causal relationship"**

between ozone and reduced plant growth and **a "causal relationship" between ozone and reduced crop yield and quality**. In the 2013 Ozone ISA, reproduction was considered in the same category with plant growth. Increased information on metrics of plant reproduction (e.g., observed flower number, fruit number, fruit weight, seed number, rate of seed germination) and evidence for direct negative effects on reproductive tissues as well as for indirect negative effects (resulting from decreased photosynthesis and other whole-plant physiological changes) warrants a separate causality determination of **a "causal relationship" between ozone exposure and reduced plant reproduction**. Since the 2013 Ozone ISA, a large-scale multivariate analysis of factors contributing to tree mortality (1971−2005) concluded that county-level ozone concentrations averaged over the study period significantly increased tree mortality in 7 out of 10 plant functional types in the eastern and central U.S. (Section 8.4.3). This evidence, combined with observations of long-term declines of conifer forests in several high ozone regions and new experimental evidence that sensitive genotypes of aspen have increased mortality with ozone exposure, supports **a "likely to be causal relationship" between ozone exposure and tree mortality.**

In addition to effects on plants, ozone can alter ecological interactions between plants and other species including herbivores consuming ozone-exposed vegetation. Studies of insect herbivores in previous ozone assessments and newer experimental studies covering a range of species at varying levels of ozone exposure frequently show statistically significant effects; however, effects on growth and reproduction are highly context- and species-specific, and not all species tested show a response (Section 8.6). **The collective evidence supports "a likely to be causal relationship" between ozone exposure and altered herbivore growth and reproduction.** Many plant-insect interactions are mediated through volatile plant signaling compounds which plants use to signal other community members. In the 2013 Ozone ISA, a few experimental and modeling studies reported altered insect-plant interactions that are mediated through chemical signaling. New evidence from multiple studies show altered/degraded emissions of chemical signals from plants and reduced detection of volatile plant signaling compounds by insects, including pollinators, in the presence of ozone (Section 8.7). **The collective evidence supports "a likely to be causal relationship" between ozone exposure and alteration of plant-insect signaling.**

At the ecosystem scale, ozone-caused decreases in plant photosynthesis can lead to reduced ecosystem carbon content. Changes in patterns of aboveground and belowground carbon allocation associated with ozone effects on plants can alter ecosystem properties of storage (e.g., productivity, carbon sequestration) and cycling (e.g., biogeochemistry) through both experimental and modeling studies. Consistent with the conclusions of the 2013 Ozone ISA, there is **a "causal relationship" between ozone exposure and reduced productivity and a "likely to be causal relationship" between ozone and reduced carbon sequestration** (Section 8.8). As described in the 2013 Ozone ISA and new experimental studies, processes such as carbon and nitrogen cycling and decomposition in soils are indirectly affected via ozone effects on the quality and quantity of carbon supply from plants and leaf litter (Section 8.9). **Recent evidence continues to support a "causal relationship" between ozone exposure and the alteration of belowground biogeochemical cycles**. Ozone can affect water use in plants through several mechanisms including damage to stomatal functioning, loss of leaf area, and

changes in wood anatomy (e.g., vessel size and density) that can affect plant and stand evapotranspiration and may lead, in turn, to possible effects on hydrological cycling as shown through a combination of experimental data and modeling (Section 8.11). Evidence continues to support the conclusion of the 2013 Ozone ISA that, **there is a "likely to be causal relationship" between ozone and alteration of ecosystem water cycling.** In terrestrial ecosystems, ozone may alter community composition by uneven effects on co-occurring species, decreasing the abundance of sensitive species, and giving tolerant species a competitive advantage. Alteration of community composition of some ecosystems including conifer forests, broadleaf forests, and grasslands and altered fungal and bacterial communities in soils reported in the 2013 Ozone ISA is augmented by additional experimental and modeling evidence for effects in forest and grassland communities (Section 8.10); collective evidence indicates a change in the causality determination to **a "causal relationship" between ozone exposure and altered terrestrial community composition of some ecosystems.**

For effects on climate, changes in the abundance of tropospheric ozone perturb the radiative balance of the atmosphere by interacting with incoming solar radiation and outgoing longwave radiation. This effect is quantified by radiative forcing.[1] Through this effect on the Earth's radiation balance, tropospheric ozone plays a major role in the climate system and increases in tropospheric ozone abundance contribute to climate change. **Recent evidence continues to support a "causal relationship" between tropospheric ozone and radiative forcing and a "likely to be causal relationship," via radiative forcing, between tropospheric ozone and temperature, precipitation, and related climate variables** (referred to as "climate change" in the 2013 Ozone ISA; the revised title for this causality determination provides a more accurate reflection of the available evidence; Table ES-3). The new evidence comes from the Intergovernmental Panel on Climate Change (IPCC) Fifth Assessment Report (AR5) and its supporting references, as well as a limited number of more recent studies, and builds on evidence presented in the 2013 Ozone ISA. The new studies further support the causality determinations included in the 2013 Ozone ISA.

Table ES-3 Summary of causality determinations for tropospheric ozone effects on climate.

	Conclusions in 2013 Ozone ISA	Conclusions in the 2020 ISA
Radiative forcing	Causal relationship	Causal relationship
Temperature, precipitation, and related climate variables	Likely to be causal relationship	Likely to be causal relationship

[1] Radiative forcing is the perturbation in net radiative flux at the tropopause (or top of the atmosphere) caused by a change in radiatively active forcing agent(s) after stratospheric temperatures have readjusted to radiative equilibrium [stratospherically adjusted radiative forcing; Myhre et al. (2013)].

ES.5 Key Aspects of Health and Welfare Effects Evidence

There is extensive scientific evidence that demonstrates health and welfare effects from exposure to ozone. As documented by the evaluation of evidence throughout the subsequent Appendices to this ISA, the U.S. EPA carefully considers uncertainties in the evidence, the extent to which recent studies have addressed or reduced uncertainties from previous assessments, and the strengths of the evidence. Uncertainties do not necessarily change the fundamental conclusions of the literature base. In fact, some conclusions are robust to such uncertainties. Where there is clear evidence linking ozone with health and welfare effects—with or despite remaining uncertainties—the U.S. EPA makes a determination of a causal or likely to be causal relationship. The identification of the strengths and limitations in the evidence will help in the prioritization of research efforts to support future ozone NAAQS reviews.

ES.5.1 Health Effects Evidence: Key Findings

A large body of scientific evidence spanning many decades clearly demonstrates there are health effects related to both short- and long-term exposure to ozone. The strongest evidence supports a relationship between ozone exposure and respiratory health effects. The collective body of evidence for each health outcome category evaluated in this ISA is considered systematically and assessed; this assessment includes evaluation of the inherent strengths, limitations, and uncertainties in the overall body of evidence for the health outcome, resulting in the causality determinations detailed in Table ES-1.

An inherent strength of the evidence integration in this ISA is the extensive amount (in both breadth and depth) of available evidence resulting from decades of scientific research that describes the relationship between both short- and long-term ozone exposure and health effects. The breadth of the enormous database is illustrated by the different scientific disciplines that provide evidence (e.g., controlled human exposure, epidemiologic, animal toxicological studies), the range of health outcomes examined (e.g., respiratory, cardiovascular, metabolic, reproductive, and nervous system effects, cancer and mortality), and the large number of studies within several of these outcome categories. The depth of the literature base is exemplified by the examination of effects that range from biomarkers of exposure, to subclinical effects, to overt clinical effects, and even mortality.

There is strong and consistent experimental evidence linking short- and long-term ozone exposure with respiratory effects and short-term ozone exposure with metabolic health effects. However, several uncertainties should be considered when evaluating and synthesizing evidence from these studies. Experimental animal studies are often conducted at ozone concentrations higher than those observed in ambient air (i.e., 250 to >1,000 ppb) to evoke a response within a short time period. These studies are informative and the conduct of studies at these concentrations is commonly used for identifying potential human hazards. There are also substantial differences in exposure concentrations and exposure durations between animal toxicological and controlled human exposure studies. Additionally, a number of animal toxicological studies are performed in rodent models of disease states, while controlled human exposure studies generally are conducted in healthy individuals. Controlled human exposure studies do not

typically include unhealthy or diseased individuals for ethical reasons; therefore, this exclusion represents an important uncertainty to consider in interpreting the results of these studies (i.e., that other individuals may be more sensitive and at risk to ozone than those in the study groups). Additional factors that differ between human and experimental animal exposures include: exposure concentration and disease status; differences in physiology (e.g., rodents are obligate nose breathers); differences in the duration and timing of exposure (e.g., rodents are exposed typically during the day, during their resting cycle, while humans are exposed during the day when they are normally active); and differences in the temperature at which the exposure was conducted. These factors may contribute to any lack of coherence between results of experimental animal and human studies. Despite these factors, there is consistent and coherent evidence that spans scientific disciplines for respiratory and metabolic health effects.

Epidemiologic studies contribute important evidence supporting the relationship between short- and long-term ozone exposure with respiratory effects. Although susceptible to chance, bias, and other potential confounding due to their observational nature, epidemiologic studies have the benefit of evaluating real-world exposure scenarios and can include sensitive populations that cannot typically be included in controlled human exposure studies. Innovations in epidemiologic study designs and methods have substantially reduced the role of chance, bias, and other potential confounders in well-designed, well-conducted epidemiologic studies. The most common source of uncertainty in epidemiologic studies of ozone is exposure measurement error. The exposure assignment methods used in short- and long-term ozone exposure epidemiologic studies have inherent strengths and limitations, and exposure measurement errors associated with those methods contribute bias and uncertainty to health effect estimates. For short-term exposure studies, exposure measurement error generally leads to underestimation and reduced precision of the association, whereas in long-term exposure studies exposure measurement error has the potential to bias effect estimates in either direction, although it is more common that they are underestimated. Furthermore, disentangling the effects of short-term ozone exposure from those of long-term ozone exposure (and vice versa) is an inherent uncertainty in the evidence base. When combined with coherent evidence from animal toxicological and controlled human exposure studies, the epidemiologic evidence can support and strengthen determinations of the causal nature of the relationship between health effects and exposure to ozone at relevant ambient air concentrations.

ES.5.2 Welfare Effects Evidence: Key Findings

The collective body of evidence for each welfare endpoint evaluated in this ISA was carefully considered and assessed, including the inherent strengths, limitations, and uncertainties in the overall body of evidence, resulting in the causality determinations for ecological effects detailed in Table ES-2 and effects on climate in Table ES-3. A large body of scientific evidence spanning more than 60 years clearly shows effects on vegetation due to ozone exposure. Decades of research on many plant species confirm effects on visible foliar injury, plant growth, reproduction and yield. The use of visible foliar injury to identify phytotoxic levels of ozone is an established and widely used methodology. There are robust exposure-response functions for reduced growth and yield (i.e., from carefully controlled

experimental conditions, involving multiple concentrations and based on multiple studies) for about a dozen important tree species and a dozen major commodity crop species. Newer evidence supports a role for ozone in tree mortality and shifts in community composition of forest tree and grassland species. While the effect of ozone on vegetation is well established in general, there are some knowledge gaps regarding precisely which species are sensitive, what exposures elicit adverse responses for many species and how plant response changes with age and size.

There is high certainty in ozone effects on impairment to leaf physiology as mechanisms for effects at higher levels of biological organization (i.e., from the cellular level through individual organisms to the level of communities and ecosystems) and how those can ultimately affect aboveground and belowground processes such as productivity, carbon sequestration, biogeochemical cycling, and hydrology. However, ecosystems are inherently complex, and it is difficult to partition observed responses within a suite of multiple stressors. Scaling ozone effects to the ecosystem level remains a challenge, but there is a large body of knowledge of how ecosystems work through ecological observations and models. Interactive effects in natural ecosystems with multiple stressors (e.g., drought, disease) are difficult to study, but some have been investigated using different statistical methods. Although models and methods for characterizing ecosystem-level responses to ozone are accompanied by inherent uncertainties, more research will strengthen understanding of scaling across different levels of biological organization.

There are multiple pathways in which ozone can affect plant-insect interactions. Studies that characterize volatile plant signaling compounds in ozone-enriched environments and assess insect response to altered chemical signals suggest that ozone alters scent-mediated interactions in ecological communities. A relatively small number of insect species and plant-insect associations have been assessed, and there are knowledge gaps in the mechanisms and consequences of modulation of signaling by ozone. There are multiple studies demonstrating ozone effects on fecundity and growth in insects that feed on ozone-exposed vegetation. However, no consistent directionality of response is observed across studies and uncertainties remain in regard to different plant consumption methods across species and the exposure conditions associated with particular severities of effects.

Changes in the abundance of tropospheric ozone affect radiative forcing, and thus tropospheric ozone is considered an important greenhouse gas. The recent IPCC AR5 estimates global tropospheric ozone radiative forcing to be 0.40 (0.20 to 0.60) W/m^2 and recent studies reinforce the AR5 estimates. Consistent with previous estimates, the effect of global, total tropospheric ozone increases on global mean surface temperature, through its impact on radiative forcing, continues to be estimated at roughly 0.1 to 0.3°C since preindustrial times with larger effects regionally. Some new research has explored certain additional aspects of the climate response to ozone radiative forcing beyond global and regional temperature change. Specifically, ozone changes are understood to have impacts on other climate metrics such as precipitation and atmospheric circulation patterns, and new evidence has continued to support and further quantify this understanding.

While the warming effect of tropospheric ozone in the climate system is well established in general, precisely quantifying changes in surface temperature due to tropospheric ozone changes, along with related climate effects, requires complex climate simulations that include all relevant feedbacks and interactions. For example, trends in free tropospheric ozone and upper tropospheric ozone (where radiative forcing is particularly sensitive to changes in ozone concentrations) are not captured well by models. In addition, substantial variation exists across models. Such modeling uncertainties make it especially difficult to provide precise quantitative estimates of the climate effects of regional-scale ozone changes. Uncertainties in estimates of preindustrial ozone concentrations represent another important source of uncertainty in climate effects resulting from long-term ozone concentration changes.

ES.6 References

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