Technical Support Document (TSD)
for the Final Revised Cross-State Air Pollution Rule Update
for the 2008 Ozone Season NAAQS

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Estimating $PM_{2.5}$- and Ozone-Attributable Health Benefits

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1 INTRODUCTION

1.1 BENEFITS ANALYSIS BACKGROUND

The EPA's *Guidelines for Preparing Economic Analyses* describe the purpose of benefit-cost analysis (BCA), related economic analyses, and the best-practices for conducting them (U.S. EPA, 2014). As described in the *Guidelines*, the fundamental objective of a BCA is to determine whether those who experience a net gain from a regulatory action can potentially compensate those who experience a net loss and remain no worse off. These gains and losses are measured by an individual's willingness to pay (WTP) for, or willingness to accept, changes attributable to the regulatory action. Consistent with economic theory, the WTP for reductions in exposure to an environmental hazard, like $PM_{2.5}$ or O_3, depends on the expected effect of those reductions on human health. BCA is the primary tool used for regulatory analysis and is used to inform the decision of whether the benefits of an action are likely to justify the costs (EO 12886, 1993, OMB, 2003).

Estimating the health benefits of reductions in $PM_{2.5}$ and O_3 exposure in a BCA begins with estimating the change in exposure for each individual and then estimating the change in each individual's risks for those health outcomes affected by exposure. The benefit of the reduction in each health risk is based on the exposed individual's WTP for the risk change.[1] The greater the magnitude of the risk reduction from a given change in concentration, the greater the individual's WTP, all else equal. The social benefit of the change in health risks equals the sum of the individual WTP estimates across all of the affected individuals.[2] There are various sources of uncertainty inherent in each of these steps, many of which are discussed in section 6.

There are three key information collection and assessment steps for implementing this framework for evaluating the health benefits of changes in exposure:

(1) Identifying health endpoints affected by exposure by assessing the strength of evidence,

(2) Identifying suitable empirical estimates of the magnitude of the relationship between exposure and these health endpoints, and

(3) Estimating the WTP for reductions in the risk of these health endpoints.

[1] As described in section 0, cost-of-illness (COI) estimates are used as a proxy for WTP estimates due to data limitations.

[2] BCA also often report the change in the sum of the risk, or the change in the total incidence, of a health outcome across the population. If WTP per unit of risk is invariant across individuals, the total expected change in the incidence of the health outcome across the population can be multiplied by the WTP per unit of risk to estimate the social benefit of the total expected change in the incidence of the health outcome. Also, if suitable WTP estimates for a health effect are unavailable, this effect will still, when possible, be quantified to provide a full picture of the potential benefits of a regulation.

This document describes all three steps for the purposes of estimating health benefits from changes in ambient $PM_{2.5}$ and O_3 exposure.[3]

1.2 The Relationship Between Identifying Health Endpoints for Valuation and WTP

The first step requires collecting and integrating scientific evidence from different types of studies and scientific fields (e.g., epidemiologic, controlled human exposure, and animal toxicological studies), as well as evaluating the quality of evidence and the consistency in the pattern of effects. Determining the strengths, limitations, and uncertainties in the overall evidence are key components, all of which could affect WTP, as this information is the basis of the desire to avoid or reduce $PM_{2.5}$ and O_3 exposure.

While the first and third step are presented as independent, they are related for an individual. All else equal, WTP is expected to be higher when there is stronger evidence of a causal relationship between exposure to the contaminant and changes in a health outcome (McGartland et al., 2017).[4,5] For example, in the case where there is no evidence of a potential relationship the WTP would be expected to be zero and the effect should be excluded from the analysis. Alternatively, when there is some evidence of a relationship between exposure and the health outcome, but that evidence is insufficient to definitively conclude that there is a causal relationship, individuals may have a positive WTP for a reduction in exposure to that hazard (Honeycutt, 2020, Kivi and Shogren, 2010). Lastly, the WTP for reductions in exposure to pollutants with strong evidence of a relationship between exposure and effect are likely positive and larger than for endpoints where evidence is weak, all else equal. Unfortunately, the economic literature currently lacks a settled approach for accounting for how WTP may vary with uncertainty about causal relationships.

Given these challenges, for step 1 the EPA draws its assessment of the strength of evidence on the relationship between exposure to $PM_{2.5}$ or O_3 and potential health endpoints from the Integrated Science Assessments (ISAs) that are developed for the NAAQS process. Specifically, in the $PM_{2.5}$ and O_3 benefits analysis for the final Revised Cross-State Air Pollution Rule (CSAPR) Update RIA, the EPA quantifies and monetizes all health effects that the ISA determines are "causal" or "likely to be causal," using scientific assessment methods described in the ISAs. The focus on categories identified as having a "causal" or "likely to be causal" relationship with the pollutant of interest is to estimate the pollutant-

[3] In addition to EPA's *Guidelines for Preparing Economic Analyses*, these methods and choices adhere to other relevant EPA and OMB guidance documents, EPA regulations, previous scientific advisory reviews, and available scientific information (U.S. EPA, 2014).

[4] It is also case that the third step depends on sources of uncertainty in the second step. That is, even if a causal relationship between exposure and a particular health risk were established with certainty, the precise empirical relationship between exposure and effect may not be known, and of the resulting uncertainty may influence the WTP to avoid this risk. For example, there may be parameter or model uncertainty in the empirical relationship between exposure and a health effect that would influence the WTP to avoid exposure (Bleichrodt et al., 2019, Freeman III et al., 2014). Section 5 describes how WTP estimates may be influenced by these sources of uncertainty.

[5] Here we are referring to causality as a general notion of how well established the relationship between a cause and possible effect is for the purposes of estimating WTP, and not to the specific approach for evaluating and determining causality between health effects and $PM_{2.5}$ and O_3 exposure used in the ISAs.

attributable human health benefits in which we are most confident.[6] All else equal, this approach may underestimate the benefits of $PM_{2.5}$ and O_3 exposure reductions as individuals may be WTP to avoid specific risks where the evidence is insufficient to conclude they are "likely to be caus[ed]" by exposure to these pollutants.[7] At the same time, WTP may be lower for those health outcomes for which causality has not been definitively established. This approach treats relationships with ISA causality determinations of "likely to be causal" as if they are known to be causal, and therefore benefits could be overestimated (section 6.5.2). This approach may be revisited in the future with scientific advancements and development of a theoretically consistent framework that jointly accounts for causal uncertainty and individuals' WTP for reducing uncertain health impacts.

1.3 Document Purpose and Overview

This is a technical support document (TSD) to the Final Revised CSAPR Update for the 2008 Ozone (O_3) Season NAAQS rulemaking. Sections relate to the three key information collection and assessment steps presented in section 1.1 and detail the methodological approaches used for identifying new benefits assessment data inputs:

1. Establish criteria for identifying studies and risk estimates most appropriate to inform a $PM_{2.5}$ and O_3 benefit analysis for an RIA (section 2.1). Study criteria, such as study design, location, population characteristics, and other attributes, were used to identify the most suitable estimates.[8] This step precedes health endpoint identification to ensure impartial health endpoint identification and prevent identification of non-quantifiable endpoints.

2. Identify pollutant-attributable health effects for which the ISA reports strong evidence and that may be quantified in a benefits assessment (section 2.2). EPA considered new evidence reported in the recent ISAs (U.S. EPA, 2019c, U.S. EPA, 2020a) and clinically significant outcomes (e.g. premature mortality and hospital admissions) for which endpoint-specific baseline incidence data is available.

3. Collect baseline incidence and prevalence estimates (section 3) and demographic information (section 4). EPA develops either daily or annual baseline incidence and prevalence rates at the most geographically- and age-specific levels feasible for each health endpoint assessed. EPA uses population projections based on economic forecasting models developed by Woods and Poole, Inc. (Woods & Poole, 2015). The Woods and Poole (WP) database contains county-level projections of population by age, sex, and race out to 2050, relative to a baseline using the 2010 Census data.

[6] This decision criterion for selecting health effects to quantify and monetize $PM_{2.5}$ and O_3 is only applicable to estimating the benefits of exposure of these two pollutants. This decision criterion may not be applicable or suitable for quantifying and monetizing health and ecological effects of other pollutants.

[7] EPA includes an example health endpoint with a causality determination of "suggestive, but not sufficient to infer" and associated with a potentially substantial economic value in the quantitative uncertainty characterization (section 6.2.3).

[8] If recent ISAs identify more new epidemiologic studies that are better suited than the prior studies for estimating risks for endpoints whose causality did not change between the prior ISA and the current ISA (e.g. respiratory hospital admissions), we use this new epidemiologic evidence to estimate risks despite the causality conclusion not changing between the prior and most recent ISAs.

4. Develop economic unit values (section 5). To directly compare benefits estimates associated with a rulemaking to cost estimates, the number of instances of each air pollution-attributable health impact must be converted to a monetary value. This requires a valuation estimate for each unique health endpoint, and potentially also discounting if the benefits are expected to accrue over more than a single year. EPA develops valuation estimates at the most age-refined level feasible for each health endpoint assessed.

5. Characterize uncertainty associated with quantified benefits estimates (section 6). Building on EPA's current methods for characterizing uncertainty, these approaches include, among others, reporting confidence intervals calculated from risk estimates, separate quantification using multiple studies and risk estimates for particularly influential endpoints (e.g., mortality risk), and approaches for aggregating and representing the results of multiple studies evaluating a particular health endpoint.[9]

[9] Study quality, inter-study heterogeneity, and redundancy issues will be taken into consideration if epidemiologic risk estimates are aggregated.

2 APPROACH TO IDENTIFYING STUDIES AND RISK ESTIMATES[10]

This section describes the criteria EPA applies to available fine particulate matter ($PM_{2.5}$) and ozone (O_3) epidemiologic studies and risk estimates to quantify air pollution-attributable health impacts for regulatory purposes, such as Regulatory Impact Analyses (RIAs). We specify the criteria used to identify the available body of epidemiologic literature potentially suitable for supporting a benefits analysis (section 2.2); apply the identification criteria to the body of available literature (section 2.2.4.3); and, finally, present the identified health endpoints and risk estimates (section 2.3) that best characterize risk to the U.S. population for health impact benefits assessments. The identification criteria precede the health endpoint identification because epidemiologic studies must meet certain minimum criteria (section 2.1.1).

2.1 STUDY AND RISK ESTIMATE IDENTIFICATION CRITERIA

We follow a systematic approach to identify the studies and risk estimates most appropriate to inform a $PM_{2.5}$ and O_3 benefit analysis for an RIA.[11] Epidemiologic studies report estimated risks of population exposure to one or more pollutants across a variety of geographic locations, age groups, population attributes, methods for estimating exposure, $PM_{2.5}$ and O_3 concentrations, time periods, study sizes, follow-up durations, and other attributes. Identification criteria, specified below, provide transparency into the scientific judgements used for identifying benefit assessment input parameters. These criteria are similar to those applied in previous EPA RIAs (Table 1) with the primary goal of identifying risk estimates that best characterize risk from $PM_{2.5}$ and O_3 exposure among the total population located throughout the U.S.[12]

2.1.1 Minimum Criteria

All studies must meet the following minimum required criteria to be considered for use in $PM_{2.5}$ and O_3 benefits assessments. These minimum criteria ensure that the subset of studies evaluated include the information necessary to justifiably quantify health effects when estimating benefits across the U.S.

1. The study must be referenced in the latest externally reviewed ISA or equivalent assessment (e.g., provisional assessment or supplement) to ensure the literature search and screening process were performed in a transparent and systematic manner and only included peer-reviewed research.

[10] What we call risk estimates in this document are results from epidemiologic studies characterizing the magnitude of exposure-related risk. This term is synonymous with several others, including concentration-response functions, effect estimates, health impact functions, risk models, and beta (β) coefficients.

[11] Epidemiological studies estimate the association between exposure to air pollution concentrations and adverse health outcomes and generally provide a relative comparison about the strength of the relationship between exposure to air pollution and the health outcome, rather than estimating the absolute health impact of an exposure (i.e. the number of avoided cases). For example, a 10 $\mu g/m^3$ decrease in daily $PM_{2.5}$ levels might be associated with a decrease in hospital admissions of 5% or a 5 ppb decrease in 8-hour maximum daily ozone concentration might be associated with a decrease in hospital admissions of 3%. A benefits analysis reports absolute values with respect to the public health impact of an exposure.

[12] See: https://www3.epa.gov/ttn/ecas/docs/ria/naaqs-pm_ria_final_2012-12.pdf

2. The study must have been conducted in either the U.S. or Canada and represent air quality conditions, affected populations, and other underlying characteristics of the U.S.[13]
3. The study must have been epidemiologic in nature, assess either $PM_{2.5}$ or O_3, and report numerical risks/hazards expressed as per a unit change in pollutant concentration to provide necessary information for health effect quantification.

2.1.2 Preferred Criteria Categories

Studies meeting the minimum criteria are then evaluated based on various factors, which we call preferred criteria, in order to identify risk estimates that best characterize risk across the U.S. These preferred criteria define other important study design features or attributes and are considered collectively (Table 1). Most criteria described below can be applied to both the studies and risk estimates, though criteria applicable only to risk estimates are noted.

Importantly, preferred criteria are established prior to study and risk estimate evaluation and these choices are based on study quality and suitability. Conversely, factors such as the magnitude of the risk estimates, are not considered when identifying studies and risk estimates.[14] Considering these factors might inadvertently bias our choice of studies or risk estimates.

Preferred criteria (Table 1) are considered simultaneously when identifying studies and risk estimates best for use in benefits assessment. Table 2 identifies specific attributes within each preferred criterion that make a particular study more (or less) suitable for identification. In practice, an identified study or risk estimate identified may not have the ideal attributes for all criteria, thus there needs to be a simultaneous assessment of the collective merits of any study or risk estimate. This means that the risk estimates ultimately identified for application in benefits assessment may not be the highest ranked in each individual preferred study criterion category, but that they rise to the top when all criteria are considered simultaneously.

Table 1. Criteria for Identifying Studies and Risk Estimates for Application in Benefits Assessment

Criteria[1]	**Description**
Study Period	Studies examining a relatively longer period of time (and therefore having more temporal coverage) are preferred because they have greater statistical power to detect effects (e.g., all else being equal, a study over a five year duration would be preferred over a study duration of one year). Studies that are more recent are also preferred because of possible changes in pollution mixes, medical care, and lifestyle over time. When identifying risk estimates, models with the broadest time coverage and overlapping air quality and health data are preferred.
Exposure Estimate	Studies estimating air quality/exposure using a combination of approaches (e.g., remote sensing techniques ground-truthed by monitoring data) are preferred over those that use a single method (e.g., monitor data), because multiple measurement methods can reduce

[13] While there are differences between the U.S. and Canada, notably with regards to the health care systems, there is considerable pollutant transport between Canada and the US, ~90% of Canadians live within ~100 miles of the US border, and ambient $PM_{2.5}$ concentrations are similar in Canada and the US (Canada, 2016, CBC, 2016, U.S. EPA, 2019b).

[14] Forest plots of the magnitudes of central risk estimates and associated confidence intervals from epidemiologic studies evaluated by the ISAs by health endpoint can be found in the respective ISAs (U.S. EPA, 2019c, U.S. EPA, 2020a). These figures illustrate the heterogeneity in the size of the reported effect among this subset of studies and risk estimates.

	exposure estimate bias and generate higher-resolution of estimates than exposure data from a single source. When available, studies of long-term/chronic exposure are preferred over short-term exposure (i.e., hours up to 1 month), considering the limitations of each exposure duration, as risk estimates based on long-term exposures may include some short-term exposure effects and provide a more comprehensive estimates of health impacts.
Study Type	Among epidemiologic studies that consider long-term exposure (e.g., one month to years), cohort studies are preferred over case-control[15] studies when estimating benefits across the U.S., as they are more representative of the overall population, and both are preferred over cross-sectional[16] or ecological[17] studies because they control for important individual-level confounding. An exception to the preference for cohort studies is for rare disease, when case-control studies may have more power and less selection bias. For short-term exposure studies, case-crossover and time series studies are preferred over cross-sectional or prevalence studies also because they are better able to control for potential confounders.
Population Attributes	Study populations representative (in terms of age, sex, race/ethnicity, etc.) of the population in which health effects are supported are preferred. The most technically appropriate measures of benefits would be based on health impact functions that cover the entire sensitive population but allow for effect modification by age, sex, race/ethnicity, or other relevant demographic factors (e.g., educational status). In the absence of effect estimates specific to age, sex, preexisting condition status, or other relevant factors, it may be appropriate to identify effect estimates that cover the broadest population to match with the desired outcome of the analysis, which for most EPA benefit-cost analyses is total national-level health impacts. Where both are available, both age-stratified and overall risk estimates should be considered for inclusion.
Study Location	U.S. or Canadian studies are used exclusively because studies conducted elsewhere may exhibit influences of potential differences in pollution characteristics, exposure patterns, medical care system, population behavior, and lifestyle. National estimates are most appropriate when benefits are nationally distributed; the impact of regional differences may be important when benefits only accrue to a single area. City-specific risk estimates from multi-city studies of hospital admissions or emergency department visits for non-fatal morbidities may be evaluated for site-specific application to the corresponding city. Canadian studies are considered when U.S study options are limited or less informative. Risk estimates with the broadest geographic coverage are preferred (e.g., multi-city studies preferred to single-city studies) because they provide a more generalizable representation of the health impacts.
Health Endpoint	To comprehensively capture the suite of attributable public health impacts and increase the power to detect effects, when estimating hospital admissions and emergency department visits, broad health endpoints are preferred over narrower, more specific endpoints. For example, more-inclusive respiratory hospital admissions endpoint would be selected over combining hospital admissions for various individual respiratory endpoints, such as asthma, long-term obstructive pulmonary disease, and respiratory infection. Please note, broad endpoint categories do not overlap (e.g., nervous system effects and respiratory effects), so there is no potential for double counting impacts.
Study Size	Studies examining a relatively large sample are preferred because they generally have more power to detect small magnitude effects. A large sample can be obtained in several ways, including through a large study population, through repeated observations on a smaller population (e.g., through a symptom diary recorded for a panel of asthmatic children) or

[15] Retrospective study in which two groups, differing in a health outcome, are identified and compared based on some hypothesized causal characteristic or exposure.
[16] Analysis of a cross-section of a population at a single point in time.
[17] Comparison of groups, rather than individuals.

	through a case crossover study design. In general, studies of larger numbers of participants and/or events are preferred.
Pollutant Concentrations	Studies evaluating air pollutant exposures closer to or below current conditions are preferred, as the risk associated with exposure may change at different pollutant concentrations and air pollution concentrations may decrease in the future,
Hazard/Risk Estimate	Studies evaluating multiple well-established statistical models adjusted for the most relevant covariates are preferred.
Inclusion of Other Pollutants	When estimating the effects of O_3 and PM (or other pollutant combinations) jointly, it is preferable to use properly specified health impact functions that include both pollutants. Using single-pollutant estimates in cases where both pollutants are expected to affect a health outcome can lead to double-counting of benefits when pollutants are correlated.
Lag Period	Lag durations were identified according to the hierarchy described in Table A-1 of the PM and O_3 ISAs. Briefly, the strongest multi-day/distributed lag periods that are more biologically plausible are preferred.
O_3 Season	Studies and risk estimates of O_3 exposure for the full year are preferred over those estimating O_3 exposures in the summer or warm season only, as O_3 concentrations can remain relatively high outside of the standard warm season in many parts of the country. As such, year-round time coverage can provide a more complete estimate of O_3 exposure health impacts.
O_3 Metric	Risk estimates based on changes in the maximum daily 8-hour average (MDA8) O_3 concentration are preferred. As discussed in the 2020 PM Policy Assessment (PA), there is considerable support from human chamber and epidemiologic studies, as well as advice from EPA's Clean Air Scientific Advisory Committee (CASAC) to support relationships between an 8-hour exposure period and short- and long-term health impacts of O_3 (U.S. EPA, 2020c).

[1] Although preferred criteria categories are not hierarchical, not all criteria are weighted equally, and expert judgement is involved.

2.1.2.1.1 Prioritizing Preferred Identification Criteria

Where Table 1 provides general information on how we determine which studies and risk estimates best characterize U.S. risk, Table 2 describes how the attributes for each of the 13 criteria are prioritized within each criteria category. Again, we use the overall study information, and studies ultimately identified generally performed better across all categories. Importantly, the order of prioritization presented in Table 2 are relative. For example, the most preferred option may be considered only slightly more preferable than the other alternative.

Table 2. Study and Risk Estimate Criteria Prioritization Order

Criteria	Prioritization Detail (In order of most to least preferred)	
Study Period	1. Most recent years with overlapping air quality and health data 2. Less recent years with partially overlapping air quality and health data 3. Studies with air quality monitoring conducted prior to 2000	
Exposure Estimate	1. Studies estimating exposure using a combination of approaches (e.g., chemical transport modeling, monitoring data, land use regression techniques, and satellite data) 2. Studies estimating exposure using some, but not all, of the above approaches (prioritized if using monitoring data and/or chemical transport modeling) 3. Studies estimating exposure using monitoring data only (prefer data from federal reference [FRM] monitors	
Study Type	*Long-Term Exposure (i.e., one month to years) Studies* 1. Cohort studies[2] 2. Case-control studies	*Short-Term Exposure (i.e., hours up to one month) Studies* 1. Case-crossover (each subject serves as own control)/Time series studies[1]

Criteria	Prioritization Detail (In order of most to least preferred)
	2. Cross-sectional/prevalence (population-level) studies
Population Attributes	Prefer studies that include broad population attributes with diverse race/ethnicities, both sexes, and broader age groups (e.g., 0-99 as opposed to only ages 0-17 or only ages 65-99)
Study Location	1. Nationwide coverage (most or all states represented), including rural areas 2. Nationwide coverage, including only urban areas 3. Multi-city and multi-state coverage 4. Multi-city or multi-state coverage 5. Single-city or -state coverage
Health Endpoints	1. **Broad** hospital admissions and emergency department visit endpoint categories (e.g., hospital admissions and emergency department visits for cardiovascular and respiratory effects as opposed to admissions or emergency department visits by individual ICD codes) and **broad** age groups (e.g., 0-99 as opposed to only 0-17 or only 65-99) 2. **Broad** hospital admissions and emergency department visit health endpoint categories and **specific** age groups 3.**Specific** hospital admissions and emergency department visit health endpoint categories and **broad** age groups 4. **Specific** hospital admissions and emergency department visit health endpoints and **specific** age groups Note: The first two options are highly preferred over the second two options
Study Size	Larger study size preferred
Pollutant Concentrations	Pollutant exposures concentrations closest to current conditions preferred.
Hazard/Risk Estimate	1. Risk estimates including the most relevant covariates (e.g., age, sex, race, education, smoking status, etc.) 2. Risk estimates including some relevant covariates 3. Risk estimates that do not include relevant covariates
Inclusion of Other Pollutants	1. Multipollutant risk estimates including other pollutants and not likely to be affected by collinearity among pollutant covariates. 2. Copollutant risk estimates including either $PM_{2.5}$ or O_3. 3. Single-pollutant risk estimates.
Lag Period	1. Distributed lag models 2. Average of multiple days (e.g., 0-2) 3. A priori lag days 4. Individual lag days, using expert judgment to identify the appropriate result to focus on considering the time course for physiologic changes for the health effect or outcome being evaluated.
O_3 Season	Annual/full-year exposures are preferred over summer/warm season-only O_3 exposures for long-term exposure-related health endpoints. Summer/warm season-only exposures are preferred over annual/full-year exposures for short-term O_3 exposure-related health endpoints.
O_3 Metric	1. 8-hour maximum O_3 2. 1-hour maximum O_3 3. 24-hour average O_3 4. Other metrics

ICD- International Statistical Classification of Diseases and Related Health Problems

[1]If a study presents both case crossover and time series results, case crossover will be identified

[2]An exception to the preference for cohort studies is for rare disease, when case control studies may have more power and less selection bias.

2.2 AVAILABLE EPIDEMIOLOGIC LITERATURE

We follow a structured and transparent process, documented below, to identifying epidemiologic literature from the body of available epidemiologic literature (section 2.1). This involves the identification of health endpoints that are both attributable to exposure (section 2.2.1) and for which we can quantify counts of cases (section 2.2.2). This literature is then reviewed using the criteria identified in Table 1 and Table 2.

2.2.1 Identification of Exposure-Attributable Health Outcomes

Our process for identifying exposure-attributable health endpoints is informed by the findings of the Integrated Scientific Assessment (ISA), which identifies broad endpoint categories causally related to pollutant exposure (section 2.2.1.1); these findings are in turn supported by plausible biological pathways of disease (section 2.2.1.2).

Each potential health endpoint must satisfy the below conditions prior to inclusion in the main benefits assessment:

- The broad endpoint category is sufficiently causally related to exposure (section 2.2.1.1)
- The specific health endpoint is a biologically plausible health effect of exposure (section 2.2.1.2)

The air quality criteria used to support the review of the National Ambient Air Quality Standards (NAAQS) undergo a structured and transparent review process for evaluating scientific information and reaching conclusions about causal determinations that are supported by the scientific information for air pollution exposures and health effects, as presented in the ISAs. To inform the NAAQS, ISAs draw upon the existing body of evidence to comprehensively evaluate and synthesize policy-relevant air pollution science. ISAs transparently identify, critically evaluate, and synthesize the current scientific literature, including epidemiology studies, making them a suitable source of 1) the causal relationships between exposure and health outcomes[18] (section 2.2.1.1), and 2) available epidemiologic literature from which to identify studies and risk estimates for consideration in benefits assessments (section 2.2.3).

A 2002 National Academy of Science review supported the use of ISAs as the basis for determining which health endpoints to include in benefits assessment, stating "the goal of health benefits analysis is to consider all relevant health outcomes" and "a comprehensive discussion of causality is not necessary for a benefits analysis" if the information is "provided in the scientific documentation for the rule-making, such as the criteria document and other related reports, and in guidance provided by EPA's Science Advisory Board" (NRC, 2002). For background, we provide a "brief review of the evidence for causality" from the most recent ISAs to "provide justification for inclusion and exclusion of specific health outcomes considered" and to acknowledge "uncertaint[ies] associated with this assumption" (section 2.2.1). This section of the TSD also provides background information with regard to potential

[18] While ISAs form causal determinations for broad endpoint categories (e.g., respiratory effects), which are generally preferred over specific health endpoints (e.g., hay fever symptoms) for comprehensive benefits assessments, they do not make causal determinations for each specific health endpoint. Instead, the ISAs provide information on the strength and consistency of the evidence supporting more specific endpoints within each broad category. The strength and consistency of evidence supporting relationships with specific health endpoints, together with the broad category causality determinations, are used when identifying specific health endpoints for inclusion in benefits assessments.

biological plausibility pathways presented in the ISAs (section 2.2.1.2) that support the causality determinations.

In addition to the causality determinations, ISAs can also serve as a curated source of pollutant-, exposure-, and endpoint-specific available epidemiologic literature. Each ISA begins with a broad, thoroughly documented literature search, the results of which undergo several screening stages to ensure included studies are within the clearly defined scope of each ISA, in order to identify the most policy-relevant science (U.S. EPA, 2015b, U.S. EPA, 2019c).[19] For example, with regard to the $PM_{2.5}$-related health effects, the 2019 PM ISA focused on epidemiologic exposures reflecting current $PM_{2.5}$ levels for health effect categories where the 2009 PM ISA concluded a "causal" or "likely to be causal" relationship (U.S. EPA, 2009).[20] As such, EPA relies on the systematic and externally reviewed ISAs for criteria pollutant health endpoints and began the process of identifying epidemiologic risk estimates for $PM_{2.5}$- and O_3-attributable benefits assessment with the literature sets identified in the 2019 PM and 2020 O_3 ISAs (U.S. EPA, 2019c, U.S. EPA, 2020a). All epidemiologic studies newly considered for use in benefits estimation are available in a separate Study Information Table, described in section 2.2.3.

2.2.1.1 ISA Causality Determinations

ISAs characterize the strength and consistency of underlying human clinical, animal toxicological, and epidemiologic evidence in making causality determinations. Generally, to estimate the pollutant-attributable human health benefits in which we are most confident, we estimate benefits resulting from health effects that we have high confidence are attributable to pollutant exposure, so we focus on categories identified as having a "causal" or "likely to be causal" relationship with the pollutant of interest in the most recently published ISA.[21] These causality determinations are applied to broad health endpoint categories (e.g., mortality, cardiovascular effects, respiratory effects, nervous system effects, metabolic effects, etc.) using a weight-of evidence approach (U.S. EPA, 2015b, U.S. EPA, 2019c), according to the rationale described below:[22]

- *Causal relationship*- Evidence is sufficient to conclude that there is a causal relationship with relevant pollutant exposures (e.g., doses or exposures generally within one to two orders of

[19] Studies identified for the 2019 PM ISA were based on the review's opening "call for information" (79 FR 71764, December 3, 2014), as well as literature searches conducted routinely to identify and evaluate "studies and reports that have undergone scientific peer review and were published or accepted for publication between January 1, 2009 and March 31, 2017. A limited literature update identified some additional studies that were published before December 31, 2017" (U.S. EPA, 2009, U.S. EPA, 2019c, Appendix, p. A-3). For the 2020 O_3 ISA that date was March 30, 2018. Relevant studies published after these dates were provisionally considered by the EPA for the final PM and O_3 NAAQS 2020 decisions but were not found to materially change any of the broad scientific conclusions regarding the health effects of PM and O_3exposure made in the 2019 PM ISA and 2020 O3 ISAs. This process ensures a thorough and transparent strategy for literature identification.

[20] The 2019 PM ISA focuses on studies conducted in areas where mean $PM_{2.5}$ concentrations are <20 $\mu g/m^3$ or, in the case of a multicity study, where more than half of the cities have concentrations <20 $\mu g/m^3$. However, studies with mean $PM_{2.5}$ concentrations exceeding 20 $\mu g/m^3$ are included if they address specific areas of uncertainty or where limitations remain in the evidence base, as identified in the 2009 PM ISA, such as copollutant confounding.

[21] This is not to imply that there may not be benefits associated with endpoints having a "suggestive of, but not sufficient to infer, a causal relationship" but rather that there is greater uncertainty associated with estimating these potential benefits (section 1.2). While these benefits are not included in the main assessment, they may be included in sensitivity analyses.

[22] See Preamble to Integrated Science Assessments, EPA/600/R-15/067, https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=347534

magnitude of recent concentrations). That is, the pollutant has been shown to result in health effects in studies in which chance, confounding, and other biases could be ruled out with reasonable confidence. For example: (1) controlled human exposure studies that demonstrate consistent effects, or (2) observational studies that cannot be explained by plausible alternatives or that are supported by other lines of evidence (e.g., animal studies or mode-of-action information). Generally, the determination is based on multiple high-quality studies conducted by multiple research groups.

- *Likely to be causal relationship*- Evidence is sufficient to conclude that a causal relationship is likely to exist with relevant pollutant exposures. That is, the pollutant has been shown to result in health effects in studies where results are not explained by chance, confounding, and other biases, but uncertainties remain in the evidence overall. For example: (1) 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 (2) animal toxicological evidence from multiple studies from different laboratories demonstrate effects but limited or no human data are available. Generally, the determination is based on multiple high-quality studies.

Conclusions made in the 2019 PM and 2020 O_3 ISAs regarding the relationships between exposure and various broad health endpoints, as well as previous determinations from the 2009 PM and 2013 O_3 ISAs, are provided below, with "causal" and "likely to be causal" judgements highlighted (Table 3 and Table 4) (U.S. EPA, 2009, U.S. EPA, 2013, U.S. EPA, 2019c, U.S. EPA, 2020a).[23] There were no "causal" or "likely to be causal" relationships for $PM_{10-2.5}$ or ultrafine particles in the 2019 PM ISA, so Table 3 focuses on $PM_{2.5}$ determinations.[24] Table 3 also highlights how the causal determinations in the 2019 PM ISA are similar to, or different from, the determinations from the 2009 PM ISA. Table 4 highlights how the new causal determinations in the 2020 O_3 ISA are similar to, or different from, the determinations from the 2013 O_3 ISA. Sections of the 2019 PM and 2020 O_3 ISAs related to "causal" and "likely to be causal" determinations were used as the basis for identifying the set of available epidemiologic literature best suited for consideration in benefit estimation (U.S. EPA, 2009, U.S. EPA, 2013, U.S. EPA, 2019c, U.S. EPA, 2020a), as discussed in more detail on section 2.2.4.3.

Table 3. Causality Determinations for $PM_{2.5}$-Related Health Effects

Exposure	Health Outcome	2009 ISA Conclusion	2019 ISA Conclusion
Long-term	Mortality[1]	Causal	Causal
	Cardiovascular Effects	Causal	Causal
	Respiratory Effects	Likely to be causal	Likely to be causal
	Nervous System Effects	None	Likely to be causal
	Cancer	Suggestive of, but not sufficient to infer	Likely to be causal
	Metabolic Effects	None	Suggestive of, but not sufficient to infer
	Male and Female Reproduction and Fertility	Suggestive of, but not sufficient to infer	Suggestive of, but not sufficient to infer

[23] Full summaries of causality determinations by exposure duration and health outcome are available in Table ES- of both the 2019 PM and 2020 O_3 ISAs.

[24] Ultrafine particles are generally considered to have an aerodynamic diameter less than or equal to 0.1 µm.

	Pregnancy and Birth Outcomes	Suggestive of, but not sufficient to infer	Suggestive of, but not sufficient to infer
Short-term	Mortality[1]	Causal	Causal
	Cardiovascular Effects	Causal	Causal
	Respiratory Effects	Likely to be causal	Likely to be causal
	Metabolic Effects	None	Suggestive of, but not sufficient to infer
	Nervous System Effects	Inadequate to infer	Suggestive of, but not sufficient to infer

[1]Total mortality includes all nonaccidental causes of mortality and is informed by findings for the spectrum of morbidity effects (e.g., respiratory, cardiovascular) that can lead to mortality. Many studies contributing to the total mortality determination assess all causes of mortality. The proportion of cause-specific deaths differs by analysis.

Table 4. Causality Determinations for O_3-Related Health Effects

Exposure	Health Outcome	2013 ISA Conclusion	2020 ISA Conclusion
Long-term	Respiratory Effects	Likely to be causal	Likely to be causal
	Cardiovascular Effects	Suggestive of a causal relationship	Suggestive of, but not sufficient to infer, a causal relationship
	Metabolic Effects	None	Suggestive of, but not sufficient to infer, a causal relationship
	Total Mortality[1]	Suggestive of a causal relationship	Suggestive of, but not sufficient to infer, a causal relationship
	Reproductive Effects	Suggestive of a causal relationship	Effects on fertility and reproduction: suggestive of, but not sufficient to infer, a causal relationship
			Effects on pregnancy and birth outcomes: suggestive of, but not sufficient to infer, a causal relationship
	Central Nervous System Effects	Suggestive of a causal relationship	Suggestive of, but not sufficient to infer, a causal relationship
Short-term	Respiratory Effects	Causal	Causal
	Total Mortality[1]	Likely to be causal	Suggestive of, but not sufficient to infer, a causal relationship
	Cardiovascular Effects	Likely to be causal	Suggestive of, but not sufficient to infer, a causal relationship
	Metabolic Effects	None	Likely to be causal
	Central Nervous System Effects	Suggestive of a causal relationship	Suggestive of, but not sufficient to infer, a causal relationship

[1]Total mortality includes all nonaccidental causes of mortality and is informed by findings for the spectrum of morbidity effects (e.g., respiratory, cardiovascular) that can lead to mortality. Many studies contributing to the total mortality determination assess all causes of mortality. The proportion of cause-specific deaths differs by analysis.

2.2.1.2 Biological Plausibility

ISAs establish causality determinations for broad health effect categories (e.g., cardiovascular effects) and provide information on the strength and consistency of the evidence supporting more specific endpoints (e.g., heart failure) within each section. Both types of information are utilized in benefits assessments. Broad causality determinations can support the use of more comprehensive endpoints

found in epidemiologic studies of hospital admissions and emergency department visits, whereas the support of specific endpoints resulting from pollutant exposure may be more relevant to incidence endpoints such as cardiac arrest.

In forming the key science judgments for each of the health effects categories evaluated, the recent ISAs draw conclusions about relationships between PM and O_3 exposure and health effects by integrating information across scientific disciplines and related health outcomes and synthesizing evidence from previous and recent studies. An advancement in these most recent ISAs is the inclusion of biological plausibility sections that are specific for each exposure duration and broad health outcome category for which causality determinations are formed. These discussions outline potential pathways along the exposure-to-outcome continuum and provide plausible links between pollutant inhalation and health outcomes at the population level. We include unedited diagrams from the biological plausibility sections of the 2019 PM and 2020 O_3 ISAs here to provide information regarding the plausibility of individual health endpoints resulting from PM and/or O_3 exposures.

Biological plausibility can strengthen the basis for causal inference (U.S. EPA, 2015b). In the recent ISAs, biological plausibility is part of the weight-of-evidence analysis that considers the totality of the health effects evidence, including consistency and coherence of effects described in experimental and observational studies. Although there is some overlap in the potential pathways between the ISA health effects chapters, each biological plausibility section is tailored to the health outcome category, pollutant, and exposure duration being evaluated within the respective section of each ISA health effects chapter. Diagrams illustrate possible pathways relating exposure to evidence evaluated in current and previous assessments, considering physiology and pathophysiology (Figure 1).[25] These diagrams portray the available evidence that supports the biological plausibility of exposures leading to specific health outcomes, but does not provide information on the weight of evidence supporting each biological pathway (section 2.2.1.2). Gaps and limitations in the evidence base, shown by the absence of a connecting arrow, correspond to gaps in the figure.

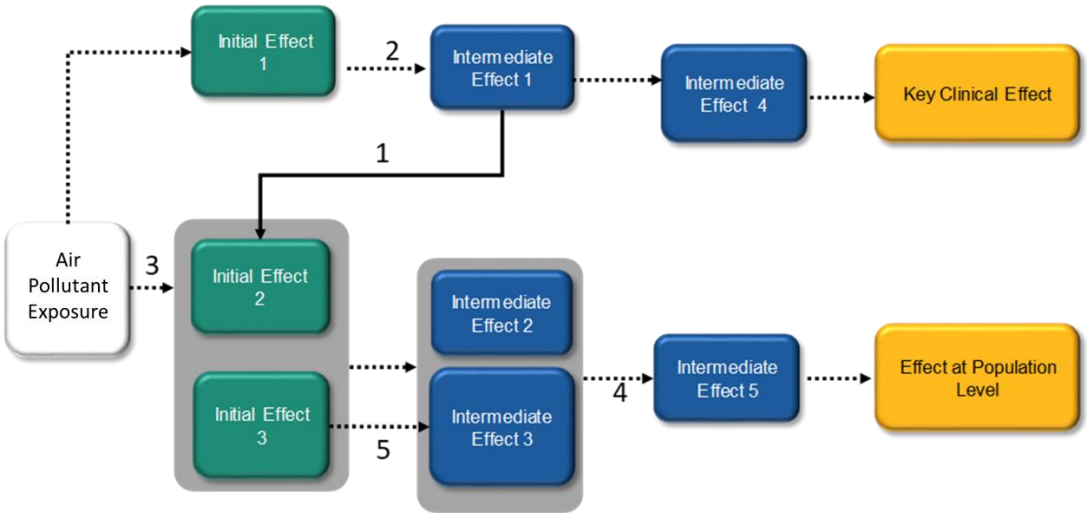
Each box represents evidence that has been demonstrated in a study or group of studies for a particular effect related to exposure. While most of the studies used to develop the figures are experimental studies (i.e., animal toxicological and controlled human exposure studies), some observational epidemiologic studies also contribute to the pathways. These epidemiologic studies are generally: 1) panel studies that measure the same or similar effects as the experimental studies (and thus provide supportive evidence) or 2) emergency department and hospital admission studies or studies of mortality, which are effects observed at the population level. The boxes are arranged horizontally, with boxes on the left side representing initial effects that reflect early biological responses and boxes to the right representing potential intermediate (i.e., subclinical or clinical) effects and potential effects at the population level. The boxes are color coded according to their position in the exposure-to-outcome continuum.

The arrows that connect the boxes indicate a potential progression of effects resulting from exposure. In most cases, arrows are dotted (Figure 1, Arrow 1), denoting a possible relationship between the effects. While most arrows point from left to right, some arrows point from right to left, reflecting progression

[25] Information in the biological plausibility diagrams includes studies identified in previous ISAs and Air Quality Criteria Documents (AQCDs).

of effects in the opposite direction or a feedback loop (Figure 1, Arrow 2). In a few cases, the arrows are solid (Figure 1, Arrow 2), indicating that progression from the upstream to downstream effect occurs as a direct result of exposure. This relationship between the boxes, where the upstream effect is necessary for progression to the downstream effect, is termed "essentiality" (OECD, 2016). Evidence supporting essentiality is generally provided by experimental studies using pharmacologic agents (i.e., inhibitors) or animal models in which the molecular pathway is obstructed. The use of solid lines, as opposed to dotted lines, reflects the availability of specific experimental evidence that exposure results in an upstream effect which is necessary for progression to a downstream effect, for example, by a genetically deficient model or a chemical inhibitor used in an experimental study involving pollutant exposure.

In the diagrams, upstream effects are sometimes linked to multiple potential downstream effects. Boxes represent the effects for which there is experimental or epidemiologic evidence related to air pollutant exposure, and the arrows indicate a proposed relationship between those effects. To illustrate the proposed relationship using a minimum number of arrows, downstream boxes are grouped together within a larger shaded box and a single arrow (Figure 1, Arrow 3) connects the upstream single box to the outside of the downstream shaded box containing multiple green boxes. Multiple upstream effects may similarly be linked to a single downstream effect using an arrow (Figure 1, Arrow 4) that connects the outside of a shaded box which contains multiple boxes, to an individual box. In addition, arrows sometimes connect one individual box to another individual box that is contained within a larger shaded box (Figure 1, Arrow 2) or two individual boxes both contained within larger shaded boxes (Figure 1, Arrow 5). Thus, arrows may connect individual boxes, groupings of boxes, and individual boxes within groupings of boxes depending on the proposed relationships between effects represented by the boxes. Population level effects generally reflect results of epidemiologic studies. When there are gaps in the evidence base, there are complementary gaps in the figure and the accompanying text below.



Note: For additional information, please refer to the original biological plausibility diagrams in the ISAs (U.S. EPA, 2019c, U.S. EPA, 2020a).

Figure 1. Illustrative Diagram of Potential Biological Pathways of Health Effects Following Pollutant Exposure.

2.2.1.2.1 $PM_{2.5}$-Attributable Endpoints and Biological Plausibility

Below are the ISA biological plausibility diagrams for $PM_{2.5}$ and O_3 endpoints judged to have either a "causal" and "likely to be causal" relationship with pollutant exposure in the 2019 PM and 2020 O_3 ISAs, as well as information on which of the endpoints identified in the diagrams have or have not been previously included in benefits assessments. These diagrams have been reproduced verbatim from the ISAs, for the convenience of the reader, and no new independent judgements are rendered regarding biological plausibility in this TSD. Although it is not possible to develop a biological plausibility diagram for total mortality, taken together, the individual endpoint-specific biological plausibility diagrams each provide potential pathways by which $PM_{2.5}$ exposures could result in mortality.

2.2.1.2.1.1 Cardiovascular Effects

The 2019 PM ISA diagram of biological pathways for cardiovascular effects following short-term $PM_{2.5}$ exposure includes emergency department visits and hospital admissions as population level effects, for which EPA has historically presented benefits impact estimates (Figure 2). The diagram also includes mortality as a key endpoint, which EPA has not included in benefits estimates due to the possibility of overlap with all-cause mortality impacts from long-term exposure resulting in double counting.

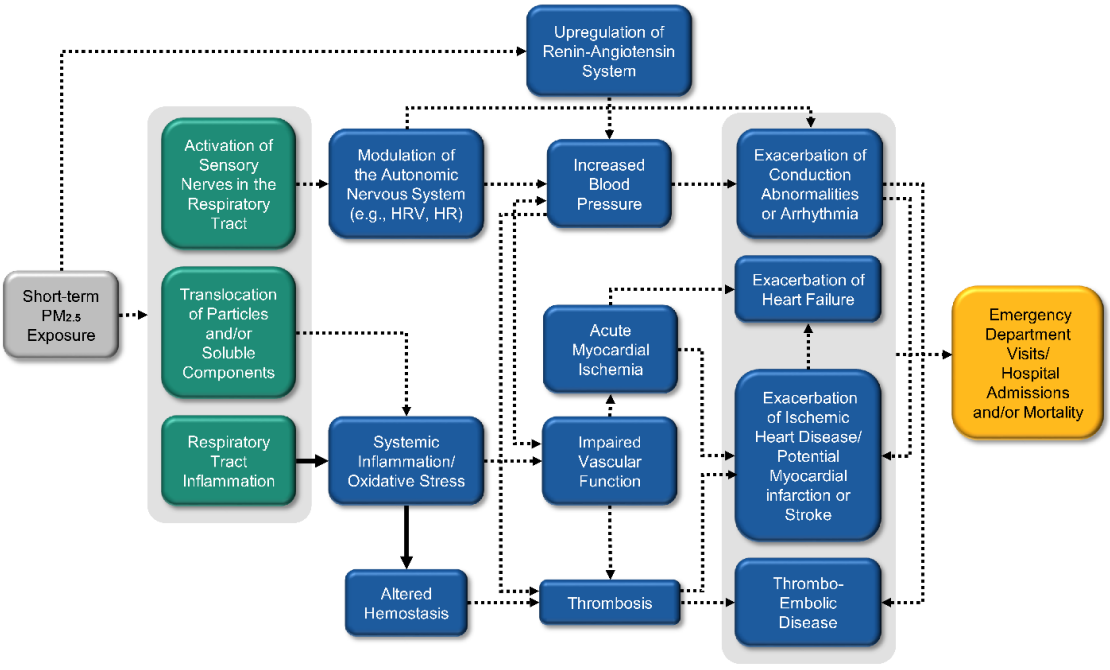


Figure 2. Potential Biological Pathways for Cardiovascular Effects Following Short-Term $PM_{2.5}$ Exposure

The 2019 PM ISA diagram of biological pathways for cardiovascular effects following long-term $PM_{2.5}$ exposure includes acute myocardial infarctions (AMI; heart attacks) and mortality, which EPA has historically presented benefits impact estimates for, and conductance abnormalities/arrhythmia, heart failure, stroke, and thromboembolic disease, which have not been included in previous benefits estimates (Figure 3).

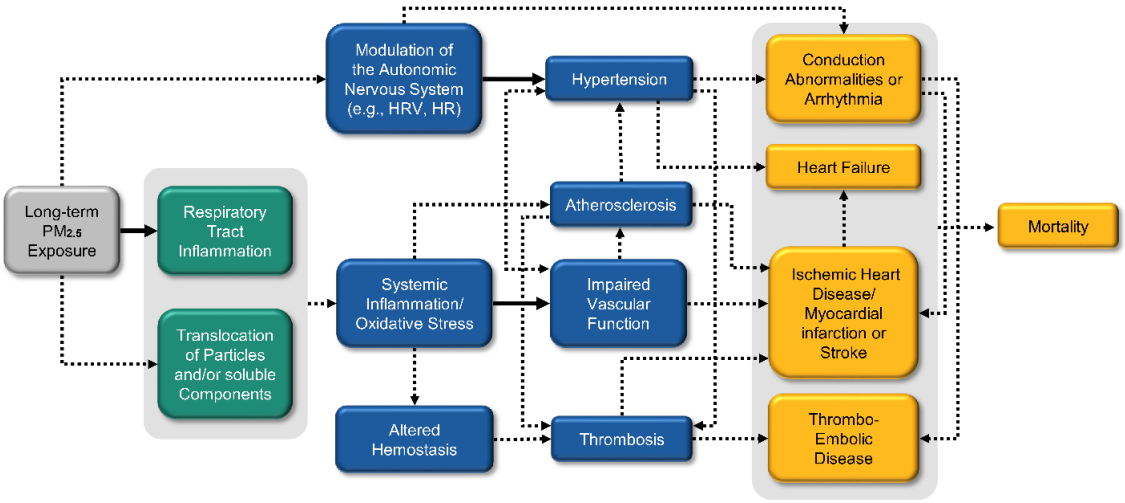


Figure 3. Potential Biological Pathways for Cardiovascular Effects Following Long-Term $PM_{2.5}$ Exposure

2.2.1.2.1.2 Respiratory Effects

The 2019 PM ISA diagram of biological pathways for respiratory effects following short-term $PM_{2.5}$ exposure includes emergency department visits and hospital admissions for asthma exacerbation/symptoms, chronic obstructive pulmonary disease (COPD), and respiratory infections as key population level health endpoints, for which EPA has historically presented benefits impact estimates (Figure 4).

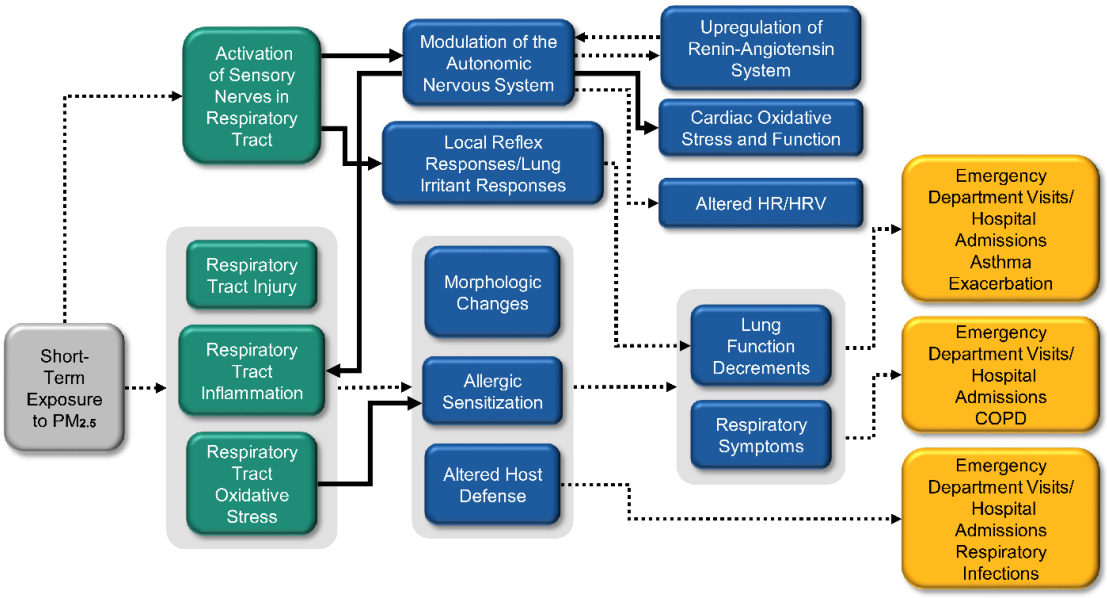


Figure 4. Potential Biological Pathways for Respiratory Effects Following Short-Term $PM_{2.5}$ Exposure

The 2019 PM ISA diagram of biological pathways for respiratory effects following long-term $PM_{2.5}$ exposure includes asthma development/onset and impaired lung function, for which we have not previously presented benefits impact estimates (Figure 5).

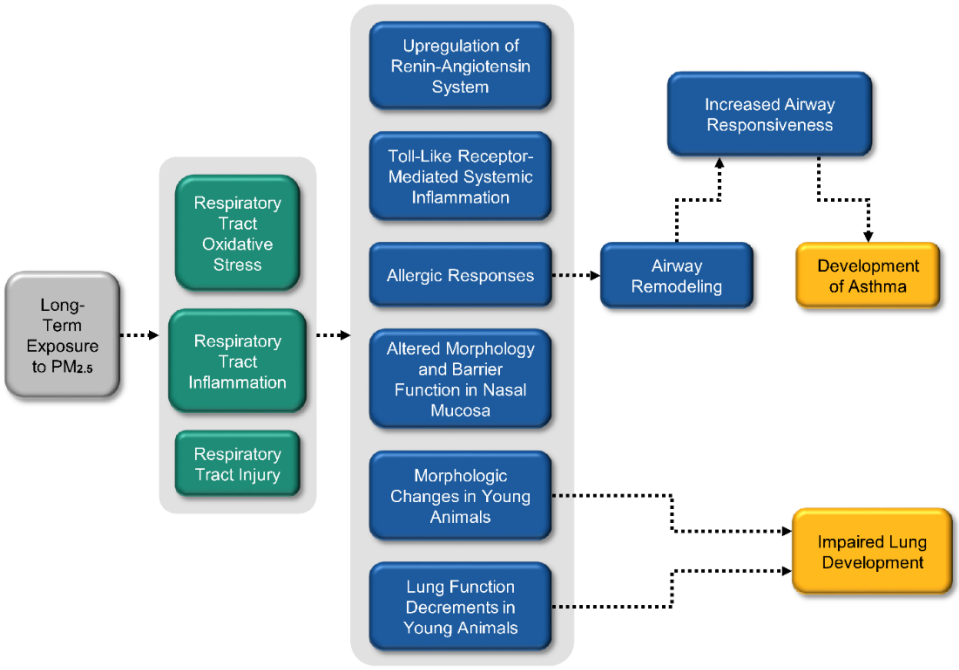


Figure 5. Potential Biological Pathways for Respiratory Effects Following Long-Term $PM_{2.5}$ Exposure

2.2.1.2.1.3 Cancer

The diagram of biological pathways of cancer following long-term $PM_{2.5}$ exposure is provided (Figure 6)., This relationship was "suggestive" in the 2009 PM ISA and "likely to be causal" in the 2019 ISA (U.S. EPA, 2009, U.S. EPA, 2019c).

As cancer is a long-term disease, the 2019 PM ISA did not provide a diagram of biological pathways for cancer following short-term $PM_{2.5}$ exposure.

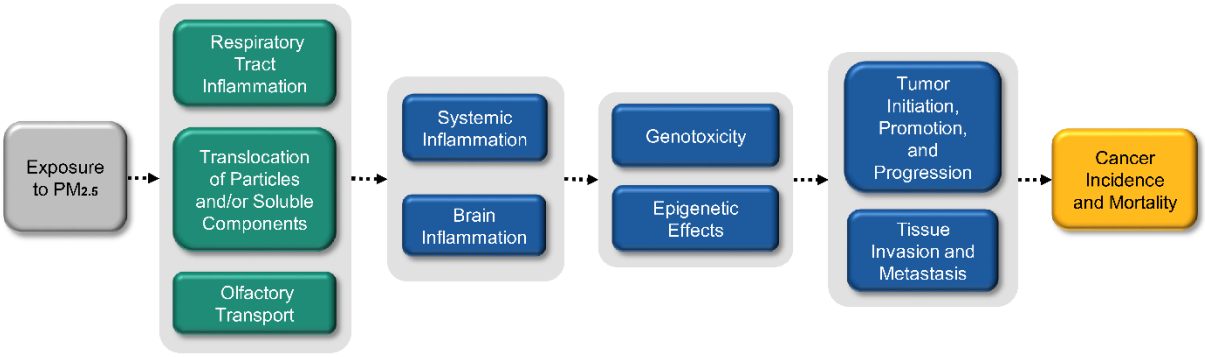


Figure 6. Potential Biological Pathways for Cancer Effects Following Long-Term $PM_{2.5}$ Exposure

2.2.1.2.1.4 Nervous System Effects

The 2019 PM ISA diagram of biological pathways for nervous system effects following long-term $PM_{2.5}$ exposure includes neurodevelopmental disorders, Parkinson's and Alzheimer's disease hospital admissions and emergency department visits, cognitive decrements/behavioral effects, and cognitive

issues (Figure 7). Please note, the weight of evidence supporting each potential is not equivalent and additional information can be found in the 2019 PM ISA (U.S. EPA, 2019c). As the previous nervous system effect ISA determination did not rise to the "causal" or "likely to be causal" level, EPA has not previously included any nervous system endpoints in benefits impact estimates.

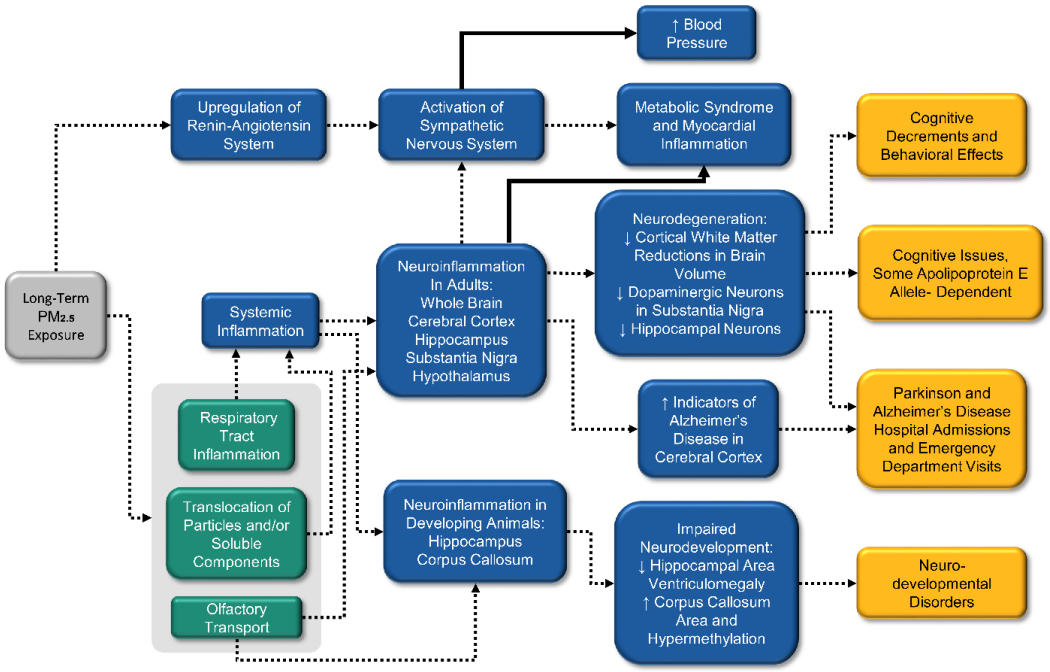


Figure 7. Potential Biological Pathways for Nervous System Effects Following Long-Term $PM_{2.5}$ Exposure

2.2.1.2.2 O_3-Attributable Endpoints and Biological Plausibility

2.2.1.2.2.1 Respiratory Effects

The 2020 O_3 ISA diagram of biological pathways for respiratory effects following short-term O_3 exposure includes emergency department visits and hospital admissions for asthma exacerbation/symptoms and respiratory infections, for which we have historically presented benefits impact estimates, and lung function decrements, which EPA has not previously estimates associated benefits (Figure 8). Although respiratory mortality is supported as a key clinical effect of short-term ozone exposure in the ISA text and should be included in this diagram, it was mistakenly left out due to the expedited timeline of the 2020 O_3 ISA.[26]

[26] This information was obtained through conversations with the authors of the 2020 O_3 ISA.

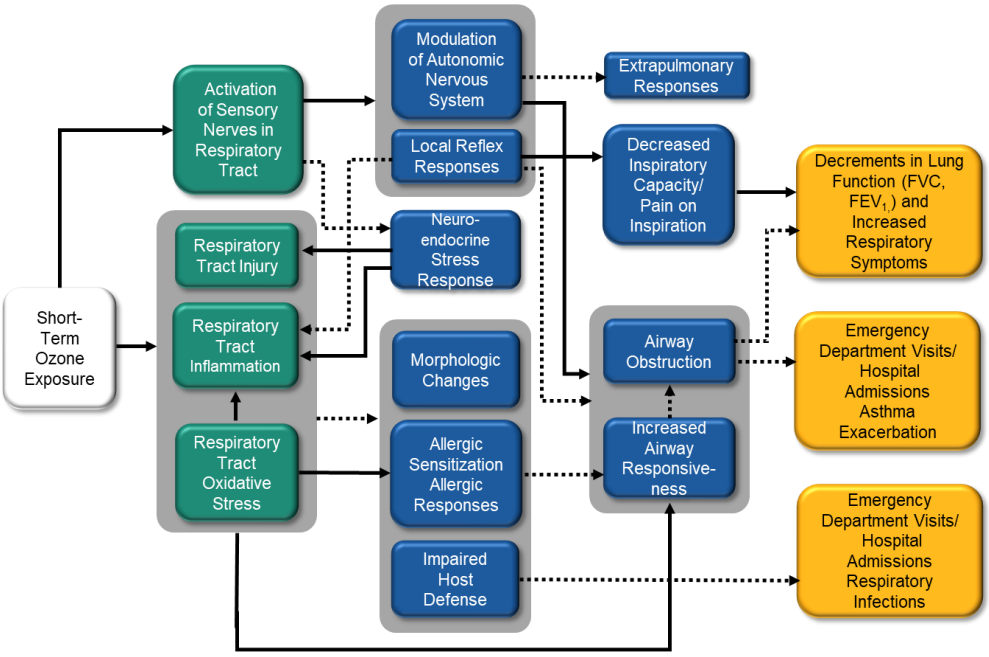


Figure 8. Potential Biological Pathways for Respiratory Effects Following Short-Term O_3 Exposure

The 2020 O_3 ISA diagram of biological pathways for respiratory effects following long-term O_3 exposure includes mortality, which EPA has included in prior benefits assessments, and asthma development/onset, fibrotic- or emphysema-like disease/COPD, and altered lung development, which EPA has not previously included in benefits impact estimates (Figure 9).

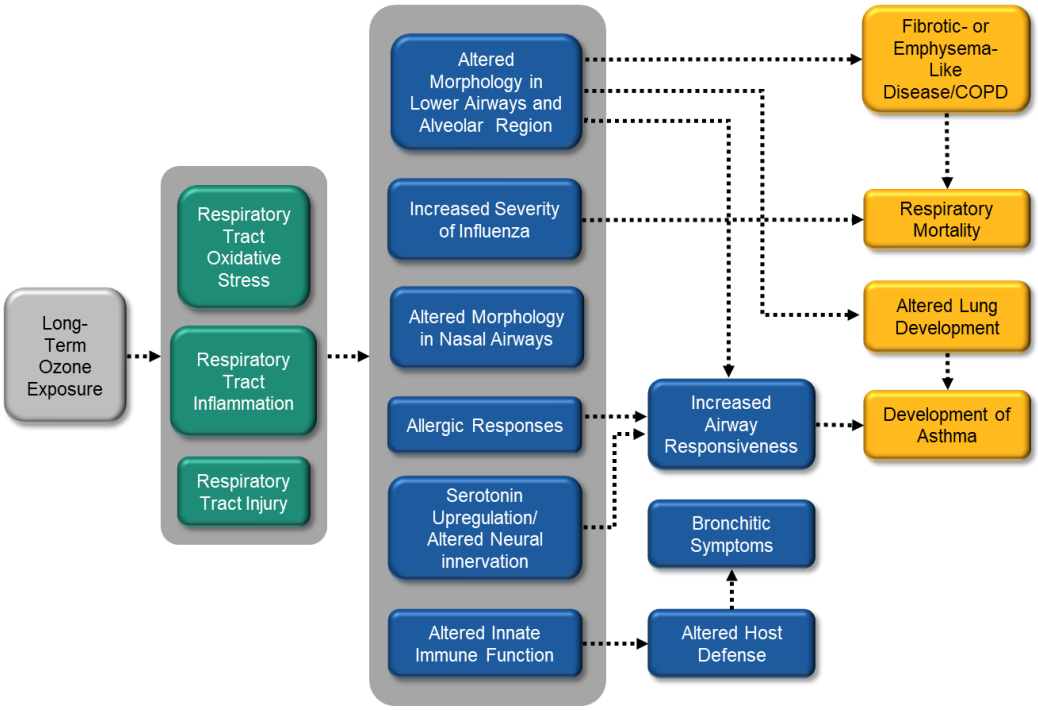


Figure 9. Potential Biological Pathways for Respiratory Effects Following Long-Term O_3 Exposure

2.2.1.2.2.2 Metabolic Effects

The 2020 O_3 ISA concluded that short-term exposure was likely to cause metabolic effects and long-term exposure was suggestive of a causal relationship. Neither short- nor long-term causal determinations were made for metabolic effects in the 2013 O_3 ISA. The ISA diagram of biological pathways for metabolic effects indicates that long-term O_3 exposure leads to complications related to diabetes and changes or contributors to metabolic syndrome, which EPA has not previously included in benefits assessments.

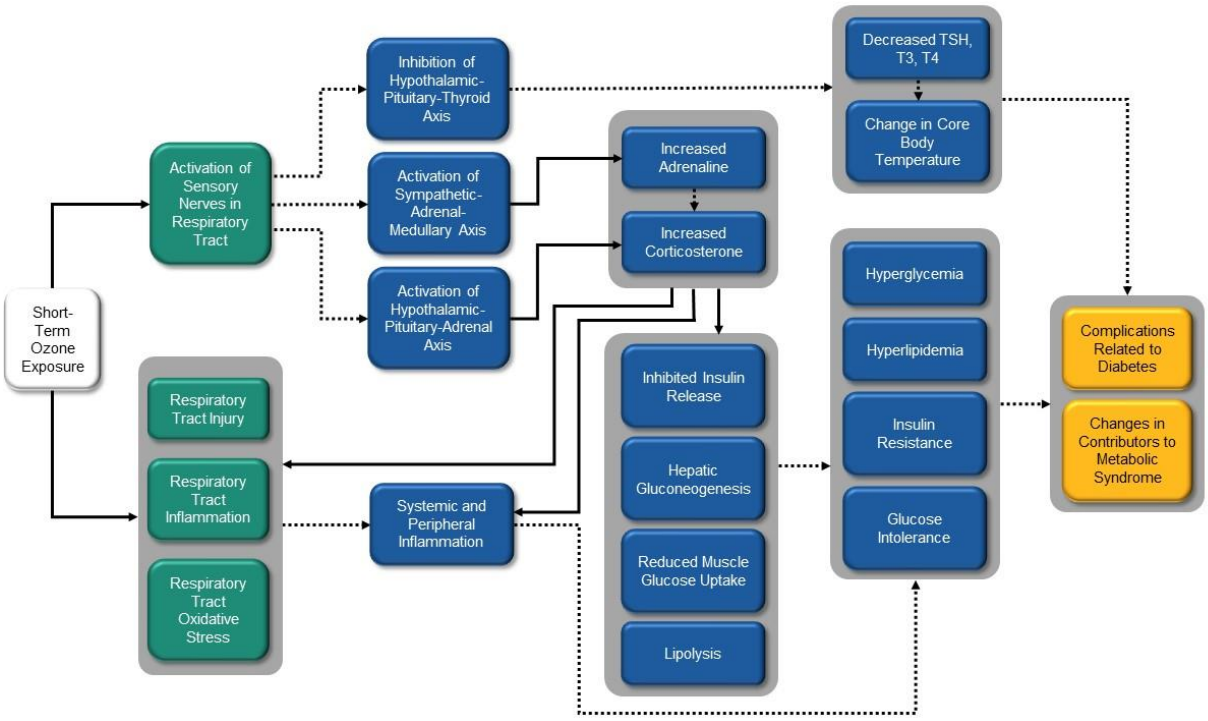


Figure 10. Potential Biological Pathways for Metabolic Effects Following Short-Term O_3 Exposure

2.2.2 Identification of Quantifiable Health Outcomes[27]

Health endpoints referenced in the latest externally reviewed ISA or equivalent assessment include both subclinical and clinically relevant endpoints. However, health impacts assessments tend to focus on quantifying the number of instances of clinically relevant endpoints (e.g., mortality, hospital admissions, and disease onset/development) and not subclinical endpoints (e.g., inflammation, oxidative stress, changes in circulation biomarkers, or changes in heart or lung function) for several reasons.

1. Specific baseline event incidence, or the amount of a particular health endpoint present within the population, is required when using epidemiologic risk estimates to project health impacts of changes in air quality. Baseline incidence data is more likely to be available for clinically relevant health endpoints (e.g., hospital admissions for cardiovascular ICD codes 390-459 or the

[27] This approach is consistent with the "effect by effect" approach described in the benefits chapter of the *Guidelines for Preparing Economic Analyses* (U.S. EPA, 2014). Quantification is treated as separable from monetization given resource and data limitations (section 1.2).

prevalence of asthma in children) then for subclinical endpoints (e.g., forced expiratory volume or hypertension).

2. Quantifying subclinical endpoints involve additional uncertainties when relating upstream subclinical effects with clinically relevant downstream health impacts. This does not mean that subclinical health impacts of $PM_{2.5}$ and O_3 do not exist. In fact, considerably more instances of pollutant-attributable subclinical effects than clinically relevant effects would be expected.

Although causal determinations are made for broad health endpoint categories (e.g., cardiovascular effects), the ISAs do review support for specific endpoints (e.g., acute myocardial infarctions) (section 2.2.1.2). Evidence associating specific health endpoints falling under broad health endpoints with "likely to be causal" or "causal" relationships with air pollution exposures are used to identify comprehensive, but not overlapping, health endpoints, when suitable studies for quantification based on the criteria identified above are available.

2.2.3 Study Information Table

Extensive and comprehensive study information is provided for transparency regarding study comparisons and identification for benefits assessment. Specific study information, corresponding to the preferred criteria in section 2.1.2, is available for all endpoint-specific, ISA-derived epidemiologic studies newly considered for use in the main and sensitivity benefits estimation in a separate Excel file titled *Study Information Table for the Estimating $PM_{2.5}$- and Ozone-Attributable Health Benefits TSD*.[28,29] Specific studies are listed once per pollutant health endpoint.

Descriptions of the specific types of information extracted from the studies and included in the Study Information Table are available in Table 5. Studies differed in the type and level of detail of information provided. Additionally, sometimes information was not reported (NR) by the study and is therefore not available in the Study Information Table. For example, not all studies provided information on the race, sex, age range of the study population. Please note, individual studies may be listed multiple times in the Study Information Table if they report results for multiple endpoints, but they are listed only once per pollutant endpoint.

Table 5. Study Information Tables

Column Name	Description
Endpoint Group	"Causal" or "likely to be causal" health endpoint included in benefits assessment.
Endpoint	Specific health endpoint included in benefits assessment.
HERO ID	Identifier used by the Health and Environmental Research Online (HERO) database. This database is a repository for studies and other references and is used for various peer-reviewed documents, such as ISAs and research projects.
First Author	First study author listed.
Publication Year	Year the article was published, according to PubMed.
Pollutant	$PM_{2.5}$ or O_3.

[28] Study information is kept in a separate Excel file to support ease of use.

[29] Risk estimate information tables are not provided as the identification of suitable risk estimates followed the hierarchy described in Table A-1 of the 2019 PM ISA appendix.

Study Type	Epidemiologic study design (e.g., cohort, case control, case crossover, etc.).
Meta-Analysis	Identifies meta-analyses for use when considering pooling city- or regional-specific estimates to generate an overall risk estimate.
Exposure Duration	Long-term (one month to years) or short-term (hours to less than one month) exposures.
Study Population	Cohort name or description if unnamed.
Study Size (number of participants or events)	This can take various forms, such as the number of participants, person-years, number of hospitalizations/admissions/discharges, or number of cases and controls. All information provided by the study is included.
Demographics	Demographics of the study participants, such as race/ethnicity, education level, income level, and socioeconomic status.
Ages	Ages of study participants, with maximum age of 99 reported when maximum participant age 99 and older.
Exposure Method	Summary of the type of exposure estimate technique. Monitor studies denote monitor-based studies, and often include land use regression (LUR) techniques. Hybrid studies include photochemical model and/or satellite data.
Country	Location of study population (U.S. or Canada).
Study Location	Brief description of the locations included in the study.
Health Years	Years of health data included.
Air Quality Years	Years of air quality data included. Many studies used a specific common time frame for entire sample, but some used other criteria, such as exposure over the first year of life.
Pollutant Concentrations (author-reported)	Typically, the overall mean and/or median concentrations across study areas, but sometimes provided information was at a different geographic and temporal scales (e.g., by state and over multiple years).
LRL/Minimum Exposure Concentration	The lowest reported pollutant level/concentration.
Pollutant Concentration Notes	Author-reported exposure estimation method. If multiple types of exposure estimation techniques were used for an individual pollutant, all are included.
Outcome Measure	Specific health outcome. Examples include the ICD codes used for hospital admission and emergency department visits or the criteria used to identify disease onset.
Lag Periods	For short-term studies, the time period of exposure prior to health effect.
Copollutants	Adjustments for copollutants in the risk estimates.
Covariates/Confounders	Author-reported covariates/confounders included in the risk estimate.
Statistical Technique	Analytical methods used to generate the risk estimate.
Qualitative Limitations	Summary comparison of each study to others investigating the same pollutant and specific health endpoint.
Relative Determination	Denotes which studies were identified as best characterizing risk as compared to other available studies for each pollutant endpoint.

2.2.4 Methods for Presenting Health Benefits Estimates Using Multiple Risk Estimates for a Single Endpoint

2.2.4.1 Pooling

If more than one study or risk estimate is suitable for characterizing risk across the U.S. for an individual health endpoint, we prefer to use multiple risk coefficients to the extent technically feasible. In such instances, we combine the risk estimates using pooling[30] methods in order to avoid a loss of information from multiple suitable studies; this approach is consistent with advice received from the National Academies of Sciences (NRC, 2002). Pooling yields a summary mean value estimate and confidence intervals reflecting variability across the pooled risk estimates. These pooled estimates take into account both the within-study variances and the between-study variance when weighting.

Unfortunately, the heterogeneous nature[31] of epidemiological studies often make them difficult to pool or otherwise aggregate. For example, it would be inadvisable to combine results from a long-term exposure study with a short-term exposure study. Other types of study heterogeneity that would prevent one from aggregating across studies include exposure duration (i.e., short- and long-term), some population attributes (e.g., age or race/ethnicity), health endpoint outcome measure (e.g., specific international classification of disease [ICD] codes), and study type (e.g., cohort vs case control).

Combining studies that differ in other aspects can be less straightforward, as there can be both advantages and disadvantages. For example, recent advancements in exposure estimation methods allow newer hybrid techniques to estimate pollutant concentrations at more detailed temporal and spatial scales. As the uncertainties associated with hybrid- and monitor-based exposure estimates vary and we consider the quality of the exposure estimate during study and risk estimate identification, we expect pooling risk estimates that vary by exposure technique will increase the confidence in the overall benefits estimate. We also consider pooling studies that differ in the study period, North American country, geographic area, pollutant concentrations, included covariates, or regression technique.

Conversely, while consistency between studies is generally desirable when pooling, there are some instances when it could introduce uncertainty and/or bias. For example, we would not pool multiple studies of the same cohort over different time periods, as these are not independent results—but rather different results from the same cohort. Hence, we would instead identify the most recent analysis or the analysis considering the longest time series of air quality data, so that the study population is not over-represented when estimating health impacts.[32]

[30] Pooling estimates would be accomplished by performing a meta-analysis, a statistical method of aggregating independent risk estimates to provide an overall single estimate. EPA has in the past sought to characterize the magnitude of uncertainty across risk estimates by either applying a fixed effect or random effects pooling technique to combine two or more risk estimates

[31] This is considered a strength when determining whether an outcome is causally linked to a pollutant.

[32] If multiple studies of the same cohort suitably characterize risk, multi-step pooling to avoid over-weighting is an option. This would involve first combining analyses of the same cohort and then combining with estimates from other cohorts.

2.2.4.2 Individual Alternate Risk Estimates

In situations where multiple scientifically robust risk estimates should not or cannot be pooled[33], we instead estimate incidence using each risk estimate independently. Where pooling synthesizes the results of multiple risk estimates into a single value, presenting multiple estimates from various key epidemiological studies identified by the latest ISA or equivalent could provide readers with insight to the plausible range of air pollution-attributable impacts. Therefore, if pooling is infeasible due to the issues mentioned above, we report individual results from each risk estimate suitable for characterizing risk across the U.S. for an individual health endpoint separately. Reporting a large number of individual estimates may characterize the heterogeneity associated with risk but may also make the resulting risk estimates more difficult to interpret. To keep results manageable, we may report additional estimates as a quantitative sensitivity analysis.

2.2.4.3 Systematic Identification of Epidemiologic Studies and Risk Estimates for Benefits Assessment

This section describes the systematic application of the identification criteria (section 2.1) to the body of available epidemiologic studies and risk estimates (section 2.2). Summary information on the number of available and included studies and risk estimates is presented in Table 6 and Table 7. Descriptions of endpoint-specific ISA support and available epidemiologic literature are available for each pollutant-attributable and quantifiable health endpoint.

2.2.5 $PM_{2.5}$

The following sections of the PM ISA correspond to health endpoints judged as having a "causal" or "likely to be causal" relationship with $PM_{2.5}$ exposure:

- 5.1 Short-Term $PM_{2.5}$ Exposure and Respiratory Effects,
- 5.2 Long-Term $PM_{2.5}$ Exposure and Respiratory Effects,
- 6.1 Short-Term $PM_{2.5}$ Exposure and Cardiovascular Effects,
- 6.2 Long-Term $PM_{2.5}$ Exposure and Cardiovascular Effects,
- 8.2 Long-Term $PM_{2.5}$ Exposure and Nervous System Effects,
- 10.2 [Long-Term] $PM_{2.5}$ Exposure and Cancer,
- 11.2 Long-Term $PM_{2.5}$ Exposure and Total Mortality

Following the approach to identifying available epidemiologic literature (section 2.2), we began with the 2,656 studies cited by the 2019 PM ISA. Of these, 491 studies evaluated mortality or morbidity health endpoints that the 2019 PM ISA determined as having a "causal" or "likely causal" relationship with $PM_{2.5}$ exposure and are clinically relevant (sections 2.2.1 and 2.2.2).[34] Of these, 82 studies met the minimum required criteria (section 2.1.1).[35]

As studies that evaluated broad and more inclusive hospital admissions and emergency department visit health endpoints (e.g., hospital admissions including a variety of respiratory endpoints) were preferred over studies that focused on hospital admissions or emergency department visits for specific health

[33] As an example, we often cannot pool across hazard ratios reported in long-term exposure cohort studies. The challenges associated with synthesizing the results of long-term cohort studies have been described elsewhere (Burnett et al., 2018).

[34] Mortality studies were treated slightly differently. More information is available in section 2.2.5.1.1.

[35] This number may not equal the sum of available studies in Table 6 as individual studies may present risk estimates for multiple health endpoints.

endpoints (e.g., hospital admissions for asthma only), we began by focusing on epidemiologic studies including broad hospital admissions and emergency department visits ICD-9 codes. This reflects strong support for these broad endpoints in the ISA, the desire to avoid double-counting of health benefits across categories, and recommendations from advisory board recommendations.[36] The remaining studies were sorted by health endpoint and $PM_{2.5}$ exposure relationship (i.e., short-term or long-term exposure to $PM_{2.5}$). These studies included 16 unique health endpoints (Table 6). In Table 6, the number of available studies refers to the number of North American studies meeting the minimum required criteria within each health endpoint, and a single study may be relevant to multiple endpoints. The risk estimates from the different studies for each endpoint can either be pooled (section 2.2.4.1) or kept as separate estimates (section 2.2.4.2), the latter of which is more common for mortality endpoints. The two columns to the far left provide the number of available risk estimates from each included study, as well as the number of risk estimates to be pooled or kept separate for each endpoint.

Once the studies were grouped by health endpoint, we applied the preferred criteria to obtain the final set of studies to inform each health endpoint. For each of the 16 endpoints, we performed a study ranking process based on these criteria that emphasized characteristics in Table 2. When no new epidemiologic studies of health endpoints previously supported by the ISAs were available, the risk estimates used previously were brought forward (e.g., work loss days).

[36] The Health Effects Subcommittee (HES) of the Advisory Council on Clean Air Compliance Analysis (Council) provided recommendations on the distinction between specific diagnostic codes and broad health outcome categories in 2004 (Ostro, 2004). The HES recommended "health outcome estimates that can be more closely linked to the results of epidemiologic studies. However, if in the efforts to achieve a match, the outcome specification is too narrow (e.g., "acute bronchitis" instead of "all respiratory conditions"), small numbers will seriously reduce the reliability of the analysis. Therefore, careful consideration of the diagnostic codes to use (with the related tradeoffs in uncertainty) will be an important step in constructing the baseline data sets."

Table 6. $PM_{2.5}$ Study and Risk Estimate Identification Diagram*

PM Endpoint and Exposure Duration	Studies Available	Studies Included	Ages	Risk Estimates Available	Risk Estimates Included
Mortality (LT)	2	1	Infants	1	1
	19	2	Adults and older adults	19	1
			Older adults	64	1
Cardiovascular Hospital Admissions (ST)	10	1	Children, adults, and older adults	28	7
Cardiovascular Emergency Department Visits (ST)	1	1	Children, adults, and older adults	3	1
AMI (ST)	NA	1	Adults and older adults	NA	1
Stroke (LT)	3	1	Older adults	1	1
Cardiac Arrest (ST)	3	3	Adults and older adults	12	1
				12	1
				7	1
Respiratory Hospital Admissions (ST)	13	2	Children	3	1
			Older adults	4	1
Respiratory Emergency Department Visits (ST)	10	1	Children	16	4
Asthma Onset (LT)	5	1	Children	7	1
Asthma Symptoms (ST)	8	1	Children	8	1
Allergic Rhinitis	1	1	Children	5	1
Minor Restricted Activity Days	NA	1	Adults and older adults	NA	1
Work Loss Days	NA	1	Adults and older adults	NA	1
Lung Cancer (LT)	4	1	Adults and older adults	24	1
Alzheimer's Disease (LT)	1	1	Older adults	53	1
Parkinson's Disease (LT)	3	1	Older adults	53	1

ST- short-term exposure; LT- long-term exposure; NA- not applicable due to the absence of recent available epidemiologic studies in the ISA; Risk estimates identified in the 2012 PM NAAQS RIA will continue to be utilized.
*See associated Study Information Table for specific study details.

2.2.5.1 All-Cause Mortality

The 2019 PM ISA concluded that a "causal" relationship exists between both long- and short-term $PM_{2.5}$ exposure and all-cause mortality. Specifically, the 2019 ISA states that:

> *Recent U.S. and Canadian cohort studies demonstrate consistent, positive associations between long-term $PM_{2.5}$ exposure and mortality across various spatial extents, exposure assessment metrics, and statistical techniques, and locations, where mean*

annual average concentrations are ≤12 µg/m^3. Additionally, the evidence from recent studies reduce uncertainties related to potential copollutant confounding and continues to provide strong support for a linear, no-threshold concentration-response relationship. The body of evidence for total mortality is supported by generally consistent positive associations with cardiovascular and respiratory mortality. There is coherence of effects across the scientific disciplines (i.e., animal toxicological, controlled human exposure, and epidemiologic studies) and biological plausibility for $PM_{2.5}$-related cardiovascular, respiratory, and metabolic disease, which supports the $PM_{2.5}$-mortality relationship. (U.S. EPA, 2019c, section 11.2.7)

As the biological pathways by which short- and long term $PM_{2.5}$ exposures are understood to lead to health effects are quite similar (section 2.2.1.2.1), we assume that effects found in studies of long-term exposures may include some effects of short-term exposures. Therefore, only mortality impacts from long-term $PM_{2.5}$ exposure will be quantified, so as not to overestimate impacts. This may potentially bias long-term, all-cause $PM_{2.5}$-attributable mortality impact estimates toward the null in the main benefit estimate.

Additional support for including estimates of all-cause $PM_{2.5}$ mortality, as opposed to cause-specific, comes from the recommendations of advisory boards and review panels. For example, in response to suggestions made in a 2002 National Resources Council (NRC) report, expert judgement studies of mortality impacts were conducted (NRC, 2002). The report recommended that "the main quantitative question should focus on all-cause mortality as the outcome, rather than eliciting separate concentration-response functions for specific causes of death" (IEc, 2006). Similarly, a more recent Health Effects Subcommittee (HES) of the Advisory Council on Clean Air Compliance Analysis (Council) affirmed the inclusion of all-cause long-term $PM_{2.5}$ estimate with no threshold was "sound" (Hammitt and Bailar, 2010).

2.2.5.1.1 Available Epidemiologic Literature

Whereas for all other health endpoints we began by identifying North American epidemiologic studies from the relevant ISA (U.S. EPA, 2019c, Figures 11-17 and 11-18), available literature for this health endpoint had been further reviewed by EPA in the 2020 PM Policy Assessment (PA) (U.S. EPA, 2020c section 3.2 and Figure 3-3). As part of this review, the PA identified multi-city studies and more recent reanalysis or extensions of some of the commonly used cohorts. As such, for this health endpoint we began with the 19 epidemiologic multi-city cohort studies identified in the 2020 PM PA, which all met the minimum criteria (section 2.1.1).

We separately evaluated the more limited literature available regarding $PM_{2.5}$-attibutable infant mortality (ages 0-12 months) cited in the 2009 ISA, as no more recent studies of $PM_{2.5}$-attributable all-cause infant mortality were available in the 2019 ISA. Full study information can be found in the Study Information Table.

2.2.5.1.2 Identifying Suitable Studies for Use in Benefits Assessments

The systematic identification criteria (section 1) was applied to the 19 studies of $PM_{2.5}$-attributable long-term all-cause mortality in adults, which prioritized particularly germane attributes including geographic coverage, population representativeness, and method of exposure estimation. As it is not relevant to study identification, we did not consider the risk effect magnitude as a criterion for study identification.

The 19 studies varied considerably with regards to all criteria considered. For example, study sizes ranged from the thousands to the tens of millions. Ultimately, all preferred criteria relevant to $PM_{2.5}$ factored into the identification of the studies best characterizing risk across the country, although geographic diversity, exposure estimation technique, population attributes, $PM_{2.5}$ concentrations, and inclusion of the copollutant O_3 were particularly germane. Specific information can be found in the corresponding Study Information Table.

2.2.5.1.3 Studies and Risk Estimates Identified as Most Suitable for Use in Benefits Assessments

As mortality impacts constitute such a large portion of health impacts and every study has inherent strengths and limitations, we expect to present mortality estimates using multiple cohort risk estimates. This approach is also consistent with previous RIAs (e.g., U.S. EPA, 2011b, U.S. EPA, 2011c, U.S. EPA, 2011d, U.S. EPA, 2012a, U.S. EPA, 2012b, U.S. EPA, 2015a, U.S. EPA, 2019a).

The systematic approach led to the initial identification of three studies best characterizing risk across the U.S. (Di et al., 2017b, Pope et al., 2015, Turner et al., 2016).[37,38] These three studies used data from two cohorts, a retrospective analysis of Medicare beneficiaries (Medicare) and the American Cancer Society Cancer Prevention II study (ACS CPS-II). The identification of these studies is consistent with the 2019 PM ISA, which concluded that the ACS CSP-II and Medicare cohorts provide strong evidence of the association between long-term $PM_{2.5}$ exposure and mortality with support from several additional cohort studies (U.S. EPA, 2019c). We discuss uncertainty and sensitivity considerations related to the identified mortality risk estimates in sections 6.1.2 and 6.5.[39]

2.2.5.1.3.1 Adult Mortality

2.2.5.1.3.1.1 ACS CSP-II

Two independent studies evaluated the same years of data from the large, nationwide ACS CSP-II cohort of those > 29 years old (Pope et al., 2015, Turner et al., 2016). These studies extended the follow-up period of the ACS CSP-II to 22 years (1982-2004), evaluating 669,046 participants over 12,662,562 person-years of follow up and 237,201 observed deaths. These two studies applied a more advanced exposure estimation approach than had previously been used when analyzing the ACS cohort, combining the geostatistical Bayesian Maximum Entropy framework with national-level land use regression models.

[37] The PM risk assessment, performed as part of the 2020 PM PA, included Di et al., 2017b, Turner et al., 2016, and Pope et al., 2015 as sources of key $PM_{2.5}$-attributable mortality risk estimates, further supporting their identification for benefits assessment. The 2020 PM PA cited a number of relative advantages of these studies related to the extended period of observation, the rigorous examination of model forms and effect estimates, the coverage for ecological variables, and the large dataset with regards to both population and area (U.S. EPA, 2019c).
[38] The Harvard Six Cities Study, which had been identified for use in estimating mortality impacts in the 2012 PM NAAQS RIA, was not identified using this approach due to geographic limitations (U.S. EPA, 2012b).
[39] There are several other assumptions implicit in the calculation of $PM_{2.5}$-related mortality impacts. Briefly, these include 1) an assumption of "cessation" lag in time between the reduction in PM exposure and the full reduction in mortality risk that affects the timing (and thus discounted monetary valuation) of the resulting deaths, 2) following conclusions of U.S. EPA, 2019c, we assume that all fine particles are equally potent in causing mortality, and 3) following conclusions of the U.S. EPA, 2019c, we assume that the health impact function for fine particles is linear within the range of ambient concentrations affected by these standards.

In addition to adjusting for individual-level and ecological covariates, Turner et al., 2016 also controlled for occupational $PM_{2.5}$ exposure and adjusted for the potential copollutants O_3 and nitrogen dioxide. Although the copollutant adjustment did not significantly change the hazard ratio, similar to the risk assessment performed as part of the PM PA (U.S. EPA, 2020c), we identified it as the most suitable hazard ratio when estimating health benefit impacts.[40] Thus, the total mortality risk estimate is based on the random-effects Cox proportional hazard model that incorporates multiple individual and ecological covariates[41] (relative risk =1.06, 95% confidence intervals 1.04–1.08 per 10µg/m^3 increase in $PM_{2.5}$). The relative risk estimate is identical to a risk estimate drawn from earlier ACS analysis of all-cause long-term exposure $PM_{2.5}$-attributable mortality (Krewski et al., 2009). Of note, the ACS cohort participants were recruited by approximately 77,000 ACS volunteers and may not precisely represent the overall U.S. population demographics.

A depiction of the slope and standard error of the hazard ratio associated with the identified risk estimate from the minimum to maximum $PM_{2.5}$ concentrations evaluated is provided (Figure 11). The static standard error is reflected in the proportionally constant 95% confidence intervals shown with red dashed lines, depicted as relative to the lowest reported level.

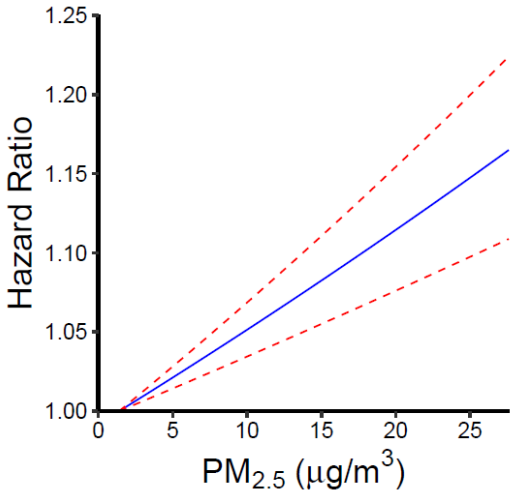


Figure 11. Functional Form of the Identified ACS CSP-II Risk Estimate

2.2.5.1.3.1.2 Medicare

The recent Di et al., 2017b analysis evaluated nearly 61 million U.S. Medicare enrollees through 460 million person-years of follow-up and roughly 22 million observed deaths. This cohort comprised approximately 15% of the total U.S. population, included people living in rural areas, and is one of the largest cohort studies published to date. The authors modeled $PM_{2.5}$ exposure across the contiguous

[40] Hazard ratios are a subtype of risk estimates.

[41] Covariates include: education; marital status; body mass index (BMI) and BMI squared; cigarette smoking status; cigarettes per day and cigarettes per day squared; years smoked and years smoked squared; started smoking at younger than 18 years of age; passive smoking (hours); vegetable, fruit, fiber, and fat intake; beer, wine, and liquor consumption; occupational exposures; an occupational dirtiness index; and six sociodemographic ecological covariates at both the postal code and postal code minus county-level mean derived from the 1990 U.S. Census (median household income and percentage of African American residents, Hispanic residents, adults with postsecondary education, unemployment, and poverty).

U.S. using a sophisticated hybrid methodology that included land use regression, satellite data, and monitor data, and resolved estimations to 1 x 1-kilometer areas. Adjustment for potential confounding by the copollutant O_3 was performed, which slightly attenuated the relationship between $PM_{2.5}$ and mortality. The authors also performed statistical testing for the potential of non-linear effects and concluded that the data supported a nearly linear concentration-response relationship with no signal of a threshold down to at least 5 µg/m^3. This study is restricted to adults over the age of 64, and thus will only be applied to that age group in benefits assessments.

In addition to the main hazard ratio, Di et al., 2017b presented three additional hazard ratios: one that excluded the copollutant O_3, one that estimated exposure using only monitor data, and one that evaluated a subset of the population experiencing lower exposures. Of these hazard ratios, only the low-exposure analysis differed substantially from the others and was considerably higher (HR = 1.136 [1.131-1.141] per 10 µg/m^3 $PM_{2.5}$). However, this analysis was restricted to person-years with both $PM_{2.5}$ exposures lower than 12 µg/m^3 and O_3 exposures lower than 50 parts per billion (ppb). Restricting the analysis in this way reduces the sample size and restricts the air quality concentrations, making estimates of risk less applicable to the entire U.S. Similarly, we prefer methods for assigning exposure that leverage both monitor and modeling techniques and models that account for potential copollutant confounding. Hence, we identified a hazard ratio from the main analysis to be the most appropriate for use (HR=1.073 [1.071-1.075] per 10 µg/m^3 $PM_{2.5}$).

A depiction of the slope and 95% confidence intervals of the hazard ratio associated with the identified risk estimate from the minimum to maximum $PM_{2.5}$ concentrations evaluated is provided (Figure 12).

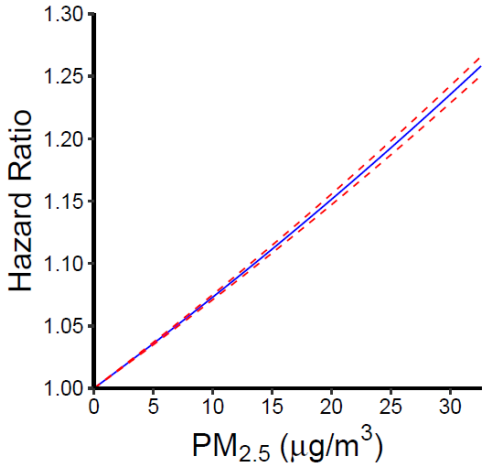


Figure 12. Functional Form of the Identified Medicare Risk Estimate

2.2.5.1.3.1.3 Summary

EPA previously used the two best estimates of mortality available, one from the ACS cohort and one from the Harvard Six Cities study. While two estimates were again identified as best characterizing risk across the U.S., their relative magnitude will depend on the populations included in the analysis (e.g., analyses of older or younger populations experiencing higher concentrations will lead to the Medicare estimate or the ACS CSP-II generating the "higher" estimate, respectively). Qualitatively, the two risk estimates identified here are both very similar to the previously used Krewski et al., 2009 estimate of mortality derived from the ACS cohort.

2.2.5.1.3.2 Infant Mortality

In addition to the adult mortality studies described above, several studies show an association between PM exposure and mortality in children under 5 years of age (U.S. EPA, 2009).[42] The 2019 PM ISA concluded that evidence exists for a stronger effect at the post neonatal period and for respiratory-related mortality, although this trend is not consistent across all studies. In addition, compared to avoided deaths estimated for adult mortality, avoided deaths for infants are significantly smaller because the number of infants in the population is much smaller than the number of adults and the epidemiology studies on infant mortality provide smaller risk estimates associated with exposure to PM. EPA has included estimates of post neonatal infant mortality from Woodruff et al., 1997 (U.S. EPA, 2012a, U.S. EPA, 2019a).

In a more recent study including a larger and more nationally-representative study size by the same group, authors examined the relationship between long-term exposure to fine $PM_{2.5}$ air pollution and post neonatal infant mortality in 3,583,495 births from 96 counties containing >249,999 residents across the U.S. between 1999-2002 using data from the National Center for Health Statistics (Woodruff et al., 2008). They linked average $PM_{2.5}$ monitoring data over the first two months of life with 6,639 post neonatal deaths, using logistic regression that incorporated generalized estimating equations (GEE) to estimate the odds ratios for all-cause and cause-specific post neonatal mortality by exposure to air pollution.[43] The study population experienced a median $PM_{2.5}$ concentration of 14.8 $\mu g/m^3$, with 25% of the population experiencing concentrations below 12 $\mu g/m^3$ and above 18.8 $\mu g/m^3$. The study included an evaluation of the appropriateness of a linear form from analysis based on quartiles of exposure and determined the linear form as a reasonable assumption. Study results included a single risk estimate of $PM_{2.5}$-attributable all-cause mortality, 1.04 (0.98-1.11) per 7 $\mu g/m^3$ (interquartile range) increase in $PM_{2.5}$.

2.2.5.2 Cardiovascular Hospital Admissions

The ISA found "generally consistent, positive associations observed in numerous epidemiologic studies of emergency department visits and hospital admissions for ischemic heart disease, heart failure, and combined cardiovascular-related endpoints" (U.S. EPA, 2019c section 6.1.16). Also, the ISA calls out cardiovascular hospital admissions as a population level health endpoint related to short-term $PM_{2.5}$ exposure (section 2.2.1.2.1.1).

2.2.5.2.1 Available Epidemiologic Literature

Ten North American epidemiologic studies of cardiovascular hospital admissions[44] were identified in section 6.1 of the PM ISA (U.S. EPA, 2019c). Relevant information related to the identification criteria, including study location, population attributes, and study period, were extracted from the studies and is available in the associated Study Information Table. The hospital admissions endpoint reports the number of events, as opposed to the number of individuals who experienced the event.

[42] For the purposes of this analysis, we only calculate benefits for infants age 0–12 months, not all children under 5 years old.

[43] Odds ratios are a subtype of risk estimates.

[44] Of the ~35 million annual hospital discharges, ~20% are related to cardiovascular effects, ~10% to respiratory effects, and ~2% to nervous system effects (https://www.cdc.gov/nchs/data/nhsr/nhsr029.pdf).

2.2.5.2.2 Identifying Suitable Studies for Use in Benefits Assessments

Relevant study information was used to identify the most nationally representative study or studies available. Study details can be found in the associated Study Information Table. The available cardiovascular hospital admissions studies predominantly included locations across the contiguous U.S. and evaluated the Medicare cohort, although two studies evaluated all ages. Few studies included health or air quality data post-2006, used hybrid exposure estimation techniques, or included O_3 as a copollutant in the risk estimates. Importantly, while all studies assessed a broad range of cardiovascular effects, the specific ICD codes included varied widely. Of the available studies, Bell et al., 2015 evaluated the most recent study period and included the most nationally representative study locations.

2.2.5.2.3 Studies and Risk Estimates Identified as Most Suitable for Use in Benefits Assessments

Bell et al., 2015 investigated the effects of short-term fine particulate matter ($PM_{2.5}$) exposure on cardiovascular health (ICD-9 410, omitting 410.x2; 410-414; 426-427; 428; 429; 430-438; and 440-448). Authors acquired data for 213 U.S. counties (1999-2010) from the Medicare Claims Inpatient Files for U.S. residents >65 years of age. Authors chose variables including sex, age, county of residence, and cause of hospital admission, as determined by ICD-9 codes. Authors collected $PM_{2.5}$ exposure data from county population-based ambient monitors from the US EPA Air Quality System and averaged for county and day. Data were present for 56.5% of study days. Bell et al. (2015) utilized Bayesian hierarchal modeling to examine the links between $PM_{2.5}$ and hospital admissions, running separate models to generate risk models for time lags (0-2 days) and season for any estimated variation in health effects. The percent increase in risk of 0.65% (95% CI: 0.48-0.83) for an increase of 10 $\mu g/m^3$ in same-day daily mean $PM_{2.5}$ concentrations came from a single pollutant model.

2.2.5.3 Cardiovascular Emergency Department Visits

The ISA found that "generally consistent, positive associations observed in numerous epidemiologic studies of emergency department visits and hospital admissions for ischemic heart disease, heart failure, and combined cardiovascular-related endpoints" (U.S. EPA, 2019c section 6.1.16). The ISA also calls out cardiovascular emergency department visits as a population level health endpoint related to short-term $PM_{2.5}$ exposure (section 2.2.1.2.1.1).

2.2.5.3.1 Available Epidemiologic Literature

Although there were several studies of both emergency department visits and hospital admissions, there was only one short-term exposure epidemiologic study specific to cardiovascular emergency department visits available in the 2019 PM ISA (U.S. EPA, 2019c).

2.2.5.3.2 Study and Risk Estimates Identified as Most Suitable for Use in Benefits Assessments

Ostro et al., 2016 investigated the association between short-term, source-specific (vehicular emissions, biomass burning, soil, and secondary NO^-_3 and SO_4 sources) $PM_{2.5}$ concentrations and emergency department visits for respiratory and cardiovascular diseases in eight cities in California from 2005 to 2008. Authors obtained medical and demographic data from the Office of Statewide Health Planning and Development in California, and diagnosis was defined with ICD-9 codes: all cardiovascular (390-459), ischemic heart disease (410–414), AMI (410), cardiac dysrhythmia (427), and heart failure (428). Ostro et al., 2016 conducted a case cross-over analysis, stratified by year and month, controlling for weather and day of the week covariates. Authors used a county-level logistic regression and random-effects meta-analysis to examine the association between source-specific $PM_{2.5}$ and emergency department visits for respiratory and cardiovascular diseases. Results indicate a positive association between vehicle $PM_{2.5}$

emissions and emergency department visits for all cardiovascular diseases. The identified excess risk estimate of 0.7% (95% CI: -0.2-1.7) per 11.4 μg/m^3 (interquartile range) daily mean $PM_{2.5}$ concentration increase came from a single pollutant model lagged by 2 days.

2.2.5.4 Cardiac Arrest (Out-of-Hospital)

The 2019 PM ISA stated that "in contrast to the studies from the previous review, recent studies have reported generally positive associations between short-term $PM_{2.5}$ exposure and out-of-hospital cardiac arrest" (U.S. EPA, 2019c, section 6.1). The ISA also called out conductance abnormalities as a key clinical effects associated with both short-and long-term $PM_{2.5}$ exposures (section 2.2.1.2.1.1).

This endpoint, like several others (e.g., lung cancer incidence, section 2.2.5.14) has a very high rate of fatality. As mortality due to any cause is captured separately (section 2.2.5.1), we focus on impacts following cardiac arrest, in the population that survive the initial event when considering this health endpoint.[45]

2.2.5.4.1 Available Epidemiologic Literature

The 2019 PM ISA included three epidemiologic studies of out-of-hospital cardiac arrest that met our minimum identification criteria (section 2.1.1).

2.2.5.4.2 Identifying Suitable Studies for Use in Benefits Assessments

All three studies each evaluated separate locations and were similar with regards to study aspects such as age range (Ensor et al., 2013, Rosenthal et al., 2008, Silverman et al., 2010). Due to differences only in the study period and locations, the three studies are pooled using the random or fixed effects pooling method for benefits assessment purposes.[46]

2.2.5.4.3 Studies and Risk Estimates Identified as Most Suitable for Use in Benefits Assessments

Ensor et al., 2013 studied the association between short-term ambient air pollution ($PM_{2.5}$ and O_3) exposure and out-of-hospital cardiac arrest. Ensor et al., 2013 gathered medical and demographic data from an Emergency Medical Services database in Houston, Texas between 2004 and 2011. Authors assessed the medical data and defined out-of-hospital cardiac arrest as emergency medical services performing chest compressions. Authors collected ambient air pollution and weather data from Texas Commission of Environmental Quality monitors and calculated hourly and daily averages for $PM_{2.5}$ and O_3. The authors used a time-stratified case crossover analysis and conditional logistic regression to interpret the data and found that with a daily increase of 6 μg/m^3 in $PM_{2.5}$, averaged from a 0- and 1-day lag, there was an increased risk of out-of-hospital cardiac arrest of 3.9% (95% CI: 0.5-7.4).

[45] Similarly, as any emergency department visits or hospital admissions resulting from cardiac arrest would be included in other endpoints (sections 2.2.5.2 and 2.2.5.3), monetized benefits of this health endpoint would not include and emergency department visits or hospital admissions costs.

[46] Random or fixed effects pooling is a method to combine two or more distributions into a single new distribution, allowing for the possibilities that either 1) a single true underlying relationship exists between the component distributions, and that differences among estimated parameters are the result of sampling error, or 2) the estimated parameter from different studies may in fact be estimates of different parameters, rather than just different estimates of a single underlying parameter, and weights for the pooling are generated via inverse variance weighting, thus giving more weight to the studies that exhibit lower variance and less weight to the input distributions with higher variance.

Silverman et al., 2010 investigated the link between short-term ambient air pollution exposure ($PM_{2.5}$, NO_2, SO_2, O_3, and CO) and out-of-hospital cardiac arrest in New York City between 2002 and 2006. Authors obtained medical data from the Emergency Medical Services of the New York City Fire Department for 8,216 subjects aged 0 to 99, average age 65.6 with slightly more men than women. Authors collected air pollution and weather data from the US EPA's Air Quality System monitors within a 20-mile radius of New York City and averaged over 24-hour periods. Authors conducted time series and case crossover analyses with 0- and 1-day lagged air pollution levels and by season. Silverman et al., 2010 found that in a single-pollutant case crossover model, each 10 $\mu g/m^3$ increase in ambient $PM_{2.5}$ resulted in a relative risk of 1.04 (95% CI: 0.99-1.08) in out-of-hospital cardiac arrest incidences 0- and 1-day prior to onset.

Rosenthal et al., 2008 examined the effects of short-term $PM_{2.5}$ exposure on out-of-hospital cardiac arrest incidence and whether these effects were connected to demographic data or presence of heart rhythm. Additionally, Rosenthal et al., 2008 compared exposure time and measurement method on the effects of short-term $PM_{2.5}$ exposure and out-of-hospital cardiac arrest incidence. Authors obtained medical data from the Wishard Ambulance Service, a local emergency medical service in Indianapolis, Indiana, from July 2, 2002 to July 7, 2006. The study defined out-of-hospital cardiac arrest using the same criteria as Ensor et al., 2013 and Silverman et al., 2010. Authors collected daily and hourly $PM_{2.5}$ concentrations from two City of Indianapolis monitoring sites and using two separate methods: the Federal Reference Method (FRM) for 24-hour filter samples, and a Federal Equivalence Method (FEM). The authors used a case crossover analysis with conditional logistic regressions in order to study the effects of short-term $PM_{2.5}$ exposure on out-of-hospital cardiac arrest incidence. Rosenthal et al., 2008 found a positive but statistically insignificant association between non-dead on arrival (non-DOA) out-of-hospital cardiac arrest cases and ambient $PM_{2.5}$ concentrations. Although they also noted a statistically significant positive association when restricted to witnessed, non-DOA out-of-hospital cardiac arrest cases, that subgroup is less applicable to the available baseline incidence rate of non-DOA out-of-hospital cardiac arrest cases. The identified risk estimate of 1.02 (95% CI: 0.92-1.12) for each 10 $\mu g/m^3$ increase in daily mean $PM_{2.5}$ concentrations lagged by 0-1 days, came from a single-pollutant model of all non-DOA out-of-hospital cardiac arrest cases.

2.2.5.5 Acute Myocardial Infarctions (AMI)

The 2019 PM ISA found that "evidence from the current review strengthens the epidemiologic results reported in the 2009 PM ISA" with respect to AMI. Specifically:

> *Several new epidemiologic studies conducted in the U.S. and Europe provide additional evidence of positive associations between short-term $PM_{2.5}$ exposure and [ischemic heart disease emergency department] visits and hospital admissions. Uncertainties noted in the last review with respect to exposure measurement error for those not living near a $PM_{2.5}$ monitor were reduced in the current review by considering recent studies that applied hybrid exposure assessment techniques that combine land use regression data with satellite measurements and $PM_{2.5}$ concentrations measured at fixed-site monitors to estimate $PM_{2.5}$ concentrations. In addition to these [emergency department] visit and hospital admissions studies, there is also evidence for ST segment depression from epidemiologic panel studies.* (U.S. EPA, 2019c).

The 2019 PM ISA also stated that "associations between long-term exposure to $PM_{2.5}$ and cardiovascular morbidity outcomes (i.e., ischemic heart disease, stroke) were observed in some studies with the most

consistent results in people with pre-existing diseases" (U.S. EPA, 2019c, section 6.2). The ISA also found that "although the results are not entirely consistent across studies or stroke subtype, some recent well-conducted studies also support a positive association between long-term exposure to $PM_{2.5}$ and stroke." Additionally, conductance abnormalities, which can lead to cardiac arrest, were called out as a key clinically relevant outcome associated with both short-and long-term $PM_{2.5}$ exposures (section 2.2.1.2.1.1).

2.2.5.5.1 Available Epidemiologic Literature

While the 2019 PM ISA did identify epidemiological studies associating AMIs with $PM_{2.5}$ exposures, the studies that passed the initial screening stage were not more suitable than those currently used for benefits estimation. One (Zhang et al., 2009) involved only postmenopausal women and the other (Delfino et al., 2011) studied a population with a history of coronary artery disease. Hence, we retained all five studies[47] used in the 2012 PM NAAQS RIA. The 2019 PM ISA did not identify any newer studies of this type so current risk estimates will continue to be used in benefit assessments (U.S. EPA, 2019c).

2.2.5.5.2 Studies and Risk Estimates Identified as Most Suitable for Use in Benefits Assessments

As no studies new to the 2019 PM ISA provided better estimates of $PM_{2.5}$ -attributable AMI risk, EPA continues to rely upon a study by Peters et al., 2001 as the basis for the impact function estimating the relationship between $PM_{2.5}$ and nonfatal heart attacks. Peters et al., 2001 exhibits a number of strengths. In particular, it includes a robust characterization of populations experiencing AMIs. The researchers interviewed patients within four days of their AMI events and, for inclusion in the study, patients were required to meet a series of criteria including minimum kinase levels, an identifiable onset of pain or other symptoms and the ability to indicate the time, place and other characteristics of their AMI pain in an interview.

Since the publication of Peters et al., 2001, a number of other single and multi-city studies have appeared in the literature. These studies include Sullivan et al., 2005, which considered the risk of $PM_{2.5}$-related hospitalization for AMIs in King County, WA; Pope III et al., 2006, based in Wasatch Range, UT; Zanobetti and Schwartz, 2006, based in Boston; and, Zanobetti et al., 2009, a multi-city study of 26 U.S. communities. Each of these single and multi-city studies, except for Pope III et al., 2006, measure AMIs using hospital discharge rates. Conversely, the Pope III et al., 2006 study is based on a large registry with angiographically characterized patients—arguably a more precise indicator of AMI. Because the Pope III et al., 2006 study reflected both myocardial infarctions and unstable angina, this produces a more comprehensive estimate of acute ischemic heart disease events than the other studies. However, unlike the Peters et al., 2001, Pope III et al., 2006 did not measure the time of symptom onset, and $PM_{2.5}$ data were not measured on an hourly basis.

As a means of recognizing the strengths of Peters et al., 2001 while also incorporating the more recent evidence found in the four single and multi-city studies, we present a range of AMI estimates. The upper end of the range is calculated using Peters et al., 2001 while the lower end of the range is the result of an equal-weights pooling of the four newer studies (Pope III et al., 2006, Sullivan et al., 2005, Zanobetti et al., 2009, Zanobetti and Schwartz, 2006).

[47] Specific study details available in the associated Study Information Table.

Peters et al., 2001 studied the relationship between increased particulate air pollution and onset of heart attacks in the Boston area from 1995 to 1996. The authors used air quality data for PM_{10}, $PM_{10-2.5}$, $PM_{2.5}$, "black carbon", O_3, CO, NO_2, and SO_2 in a case crossover analysis. For each subject, the case period was matched to three control periods, each 24 hours apart. In univariate analyses, the authors observed a positive association between heart attack occurrence and $PM_{2.5}$ levels hours before and days before onset. The authors estimated multivariate conditional logistic models including 2-hour and 24-hour pollutant concentrations for each pollutant. They found significant and independent associations between heart attack occurrence and 24-hour $PM_{2.5}$ concentrations before onset. Significant associations were observed for PM_{10} as well. None of the other particle measures or gaseous pollutants were significantly associated with AMI for the 2-hour or 24-hour period before onset. The mean age of participants was 62 years old, with 21% of the study population under the age of 50. In order to capture the full magnitude of heart attack occurrence potentially associated with air pollution and because age was not listed as an inclusion criterion for sample selection, we apply an age range of 18 and over in the risk estimate. According to the National Hospital Discharge Survey, there were no hospitalizations for heart attacks among children <15 years of age in 1999 and only 5.5% of all hospitalizations occurred in those aged 15-44 years. The odds ratio is 1.62 (95% CI: 1.13-2.34) for a 20 $\mu g/m^3$ increase in 24-hour average $PM_{2.5}$.

Pope III et al., 2006 evaluated the association between short-term exposure to $PM_{2.5}$ and acute ischemic heart disease events, including nonfatal AMI, all acute coronary events, and subsequent myocardial infarctions in individuals living in greater Salt Lake City, Utah. In a case crossover study, these ischemic events were assessed in relation to a 10 $\mu g/m^3$ increase in $PM_{2.5}$. The researchers determined that a 10 $\mu g/m^3$ increase in $PM_{2.5}$ resulted in a 4.5% increase (95% CI: 1.1-8.0) in unstable angina and myocardial infarction.

Sullivan et al., 2005 studied the relationship between onset time of acute myocardial infarction and the preceding hourly $PM_{2.5}$ concentrations in 5,793 confirmed cased of myocardial infarction through King County, Washington. In this case crossover study from 1988-1994, air pollution exposure levels averaged before onset of myocardial infarction were compared to a set of time-stratified referent exposures from the same day of the week in the month of the case event. The authors estimated that an associated risk of 1.01 (95% CI: 0.98-1.05) for myocardial infarction onset could be attributed to a 10 $\mu g/m^3$ increase in PM 2.5 the hour before the MI onset. No increased risk was found in all cases with preexisting cardiac diseases with an odds ratio of 1.05 (95% CI: 0.95-1.16). Furthermore, stratification for hypertension, diabetes, and smoking status did not modify the association between $PM_{2.5}$ and onset of myocardial infarction.

Zanobetti et al., 2009 examined the relationship between daily $PM_{2.5}$ levels and emergency hospital admissions for cardiovascular causes, myocardial infarction, congestive heart failure, respiratory disease, and diabetes among 26 U.S. communities from 2000-2003. The authors used meta-regression to examine how this association was modified by season- and community-specific $PM_{2.5}$ composition while controlling for seasonal temperature as a substitute for ventilation. For a 10 $\mu g/m^3$ increase in 2-day averaged $PM_{2.5}$, a 1.89% (95% CI: 1.34-2.45) increase in cardiovascular disease admissions, a 2.25% (95% CI: 1.10-3.42) increase in myocardial infarction admissions, a 1.85% (95% CI: 1.19-2.51) increase in congestive heart failure admissions, a 2.74% (95% CI: 1.30-4.20) increase in diabetes admissions, and a 2.07% (95% CI: 1.20-2.95) increase in respiratory admissions were observed. The relationship between $PM_{2.5}$ and cardiovascular admissions was significantly modified when the mass of $PM_{2.5}$ was high in Br, Cr, Ni, and sodium ions, while mass high in As, Cr, Mn, organic carbon, Ni and sodium ions modified the

myocardial infarction relationship and mass high in As, organic carbon, and sulfate ions modified the diabetes admission rates.

Zanobetti and Schwartz, 2006 analyzed hospital admissions through emergency department for MI (ICD-9 code 410) and pneumonia (ICD-9 codes 480-487) for associations with fine particulate air pollution in the greater Boston area from 1995- 1999. The authors used a case-crossover analysis with control days matched on temperature. Significant associations were detected for $PM_{2.5}$ with an 8.6% increase (95% CI: 1.2-15.4) in emergency myocardial infarction hospitalizations. The study looked at hospital admissions of AMI through the ER. Under the assumption that all heart attacks will end in hospitalization, we consider the endpoint as heart attack events to be consistent with other studies. In a single-pollutant model, the coefficient and standard error are estimated from the percent change in risk (8.65%) and 95% confidence interval (95% CI: 1.22-15.38%) for a 16.32 $\mu g/m^3$ increase in daily 24-hour mean $PM_{2.5}$ for an average of the 0- and 1-day lag (Zanobetti and Schwartz, 2006, Table 4).

2.2.5.6 Stroke

2.2.5.6.1 Available Epidemiologic Literature

The 2019 PM ISA included three epidemiologic studies of stroke that met the minimum identification criteria (section 2.1.1).

2.2.5.6.2 Identifying Suitable Studies for Use in Benefits Assessments

One of the available epidemiologic studies was more recent, included a larger population, evaluated long-term exposure effects, and was more representative of the U.S. with regards to both geography and population attributes than the other two studies (Kloog et al., 2012).

2.2.5.6.3 Studies and Risk Estimates Identified as Most Suitable for Use in Benefits Assessments

Kloog et al., 2012 analyzed the effects of long- and short-term $PM_{2.5}$ exposure on hospital admissions due to strokes with a new $PM_{2.5}$ exposure model in New England (Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, and Vermont) from 2000 to 2006. We use this endpoint as a surrogate for $PM_{2.5}$-attributable stroke incidence. Authors collected medical data from 67,678 adults aged 65 to 99 in the U.S. Medicare program database from 2000 to 2006. They defined all respiratory, cardiovascular disease, stroke, and diabetes based on emergency department visits and primary discharge diagnosis records. Authors used a hybrid exposure technique comprised of daily $PM_{2.5}$ concentration data from aerosol optical depth (AOD) measurements and ambient air monitors from the U.S. EPA and Interagency Monitoring of Protected Visual Improvements (IMPROVE). Authors also obtained land use regressions, meteorological data (National Climatic Data Center), and socioeconomic data (U.S. Census Bureau) matched to zip codes. Utilizing land use Poisson regression single-pollutant models, the authors found an 3.49% (95% CI: 0.09-5.18) increase in stroke incidence for a 10 $\mu g/m^3$ increase in the 7-year mean $PM_{2.5}$ concentrations.

2.2.5.7 Respiratory Hospital Admissions

After considering the relationships between specific and broad respiratory hospital admissions endpoints, the 2019 PM ISA stated that "recent studies further expand analyses with older adults, with multicity studies conducted in the U.S. providing evidence of consistent, positive associations between short-term $PM_{2.5}$ exposure and respiratory-related diseases" ((U.S. EPA, 2019c, section 5.1.6).

The ISA noted that "it is often difficult to determine whether the associations observed indicate that $PM_{2.5}$ may affect the spectrum of respiratory diseases or reflects the evidence supporting associations with specific respiratory diseases, such as asthma." Taking this into consideration, hospital admissions for asthma exacerbation/symptoms, COPD, and respiratory infections were specifically called out in the short-term $PM_{2.5}$ exposure biological plausibility diagram (section 2.2.1.2.1.2).

2.2.5.7.1 Available Epidemiologic Literature

Like the cardiovascular hospital admission/emergency department visit endpoints, several respiratory studies identified by the ISA combined the hospital admissions and emergency department endpoints. There was also a subset of studies that only considered emergency hospital admission, defined as hospital admissions that originated in the emergency department. As using either studies of emergency hospital admissions or combined emergency department and hospital admission studies would result in increased uncertainty around the economic estimate and/or with the baseline incidence data, we limited our pool of available studies to those specifically evaluating unplanned respiratory hospital admissions, of which there were 12 available studies.

2.2.5.7.2 Identifying Suitable Studies for Use in Benefits Assessments

Studies for this endpoint tended to focus on specific age groups, with approximately half focusing on older adults (>64) and none specifying ages 19-64. Importantly, studies varied widely by ICD codes, making pooling of two or more studies difficult. Considering the preferred criteria, two studies were identified, one of children and one of older adults, primarily due to the inclusion of diverse and large study locations. The single study of older adults is more informative than pooling it with other studies of the same population as it is more recent and includes exposure to lower $PM_{2.5}$ concentration levels.

2.2.5.7.3 Studies and Risk Estimates Identified as Most Suitable for Use in Benefits Assessments

Bell et al., 2015 investigated the effects of short-term fine particulate matter ($PM_{2.5}$) exposure on respiratory health (ICD-9 464-466, 480-487, 490-492, 493) in older adults (>64 years). Authors acquired data for 213 U.S. counties (1999-2010) from the Medicare Claims Inpatient Files for U.S. residents >65 years of age. Authors chose variables including sex, age, county of residence, and cause of hospital admission, as determined by ICD-9 codes. Authors collected $PM_{2.5}$ exposure data from county population-based ambient monitors from the US EPA Air Quality System and averaged for county and day. Data were present for 56.5% of study days due to the sampling schedule of the monitors. Bell et al., 2015 utilized Bayesian hierarchal modeling to examine the links between $PM_{2.5}$ and hospital admissions. They ran separate models for time lags (0-2 days) and season to determine if there were any estimated variation in health effects. The identified percent increase in risk of 0.25% (95% CI: 0.01-0.48) for an increase of 10 $\mu g/m^3$ in same-day daily mean $PM_{2.5}$ concentrations came from a single-pollutant model.

Ostro et al., 2009 estimated the association between ambient $PM_{2.5}$, EC, organic carbon (OC), NO_3, and SO_4 on hospital admissions for respiratory diseases in children ages 5 to 19. The study used the California Office of Statewide Health Planning and Development, Healthcare Quality and Analysis Division hospitalization data from six California counties for the 2000 to 2003 study period. Ostro et al., 2009 classified hospital admissions into: all respiratory disease (ICD-9 codes 460-519), asthma (ICD-9 code 493), acute bronchitis (ICD-9 code 466), and pneumonia (ICD-9 codes 480-486). They aggregated the hospital admission data to the county level to create a daily time series of admissions for each county. Authors took air quality measurements from the California Air Resources Board, which captured speciated 24-hour average pollutant measurements using a filter-based Met One Speciation Air

Sampling System. Meteorological measurements for average daily temperature and relative humidity came from the California Air Resources Board or the California Irrigation Management Information System. Authors analyzed data using a Poisson regression with time, day of the week, temperature, relative humidity, and pollutant as explanatory variables. Ostro et al., 2009 controlled for seasonality and time dependent effects by including a natural spline smoother for the daily time trend and meteorology. The identified percent increase in risk of excess risk of 4.1% (95% CI: 1.8-6.4) for a 14.6 $\mu g/m^3$ increase in daily mean $PM_{2.5}$ concentrations, lagged by 3 days, came from a single-pollutant model.

2.2.5.8 Respiratory Emergency Department Visits

After considering the relationships between specific and broad respiratory emergency department visit endpoints, the 2019 PM ISA stated that "recent studies further expand analyses with older adults, with multicity studies conducted in the U.S. providing evidence of consistent, positive associations between short-term $PM_{2.5}$ exposure and respiratory-related diseases" (U.S. EPA, 2019c, section 5.1.6).

The ISA noted that "it is often difficult to determine whether the associations observed indicate that $PM_{2.5}$ may affect the spectrum of respiratory diseases or reflects the evidence supporting associations with specific respiratory diseases, such as asthma." Emergency department visits for asthma exacerbation/symptoms, COPD, and respiratory infections were specifically called out in the short-term $PM_{2.5}$ exposure biological plausibility diagram (section 2.2.1.2.1.2).

2.2.5.8.1 Available Epidemiologic Literature

Like the cardiovascular hospital admission/emergency department visit endpoints, several respiratory studies identified by the ISA combined the hospital admissions and emergency department endpoints. As using the combined study endpoint would result in increased uncertainty around the economic estimate, we limited our pool of available studies to those specifically looking at respiratory emergency department visits for the main benefits assessment, of which there were 10 studies.

2.2.5.8.2 Identifying Suitable Studies for Use in Benefits Assessments

One study out of the 10 was more recent, provided greater geographic representation, and included all ages.

2.2.5.8.3 Studies and Risk Estimates Identified as Most Suitable for Use in Benefits Assessments

Krall et al., 2013 investigated the associations between short-term, source-specific (traffic and coal combustion) ambient $PM_{2.5}$ exposure and emergency department visits for respiratory diseases in U.S. cities (Atlanta, GA, Birmingham, AL, St. Louis, MO, and Dallas, TX). Authors obtained medical data from hospital electronic billings for emergency department visits due to respiratory disease, identified using ICD-9 codes (460-465, 466, 477, 480-486, 491, 492, 493, 496, 786.07). Authors collected $PM_{2.5}$ concentrations from one ambient air monitor in each of the four cities and gathered meteorological data from the National Climactic Data Center. Krall et al., 2013 estimated source-specific $PM_{2.5}$ using apportionment models, which separate $PM_{2.5}$ sources based on chemical composition. This model also included data on gaseous pollutant concentrations from the Community Multiscale Air Quality (CMAQ) with Tracers model. Krall et al., 2013 used Poisson time series regression models to analyze associations between short-term $PM_{2.5}$ exposure and emergency department visits for respiratory diseases. They then compared source-specific $PM_{2.5}$ exposures across cities to estimate associations with the emergency department visit data. To limit confounders, the authors adjusted models for indicator

variables, meteorological variables, and long-term trends in emergency department visits. The identified relative risk estimates of 1.005 (95% CI: 1.000-1.010) for Atlanta, GA; 1.009 (95% CI: 1.003-1.015) for Birmingham, AL; 1.008 (95% CI: 1.002-1.014) for St. Louis, MO; and 1.012 (95% CI: 1.002-1.023) for Dallas, TX were calculated from a single-pollutant model for a 9.16 $\mu g/m^3$ increase in daily mean $PM_{2.5}$ concentrations, lagged by 0 days.

2.2.5.9 Asthma Onset

The 2019 PM ISA stated that "longitudinal studies provide evidence of associations with asthma incidence in children" and found "evidence for a relationship between $PM_{2.5}$ exposure and asthma prevalence in children and childhood wheeze" (U.S. EPA, 2019c). Additionally, asthma onset was called out as a key clinically relevant health endpoint in the biological plausibility pathways included in the ISA (section 2.2.1.2.1.2) (U.S. EPA, 2019c).

2.2.5.9.1 Available Epidemiologic Literature

The final 2019 PM ISA found that "recent studies of asthma in children supplement the limited number of studies reviewed in the 2009 PM ISA and provide evidence of an association between long-term $PM_{2.5}$ exposure and asthma development in children" (U.S. EPA, 2019c). There was also evidence of $PM_{2.5}$-attributable asthma onset in adults, but results were inconsistent across studies. As a result, asthma onset in adults is not included in our main benefits assessment.

Five North American epidemiologic studies of asthma onset in children were identified in section 5.2 of the 2019 PM ISA (U.S. EPA, 2019c). Relevant information related to the identification criteria, including study location, population attributes, and study period, were extracted from the studies and is available in the corresponding Excel file.

2.2.5.9.2 Identifying Suitable Studies for Use in Benefits Assessments

Although the available asthma onset studies vary widely in all criteria considered, relevant study information was again used to identify the most nationally representative study or studies (see Excel file). Interestingly, three of the five studies were conducted in Canada.[48] One study conducted in Canada evaluated a recent and extensive time series of air quality and health data; assigned exposures to populations using a combination of monitor and remote sensing data; validated the outcome measure; observed effects with relatively low (~10 $\mu g/m^3$) $PM_{2.5}$ concentrations, and included over 30-fold the number of participants as any other study. Other available literature was also more limited with regards to population demographic and geographic diversity.

2.2.5.9.3 Study Identified as Most Suitable for Use in Benefits Assessments

Tetreault et al., 2016 investigated the relationship between childhood asthma onset and long-term pollution exposure ($PM_{2.5}$, NO_2, O_3) in Quebec, Canada. The authors obtained data from four medical-

[48] Although several key studies identified in the 2019 PM ISA come from Europe, we excluded studies outside of North America. Studies taking place in Canada were retained, as there is considerable $PM_{2.5}$ transport between Canada and the US (https://www.epa.gov/airmarkets/canada-united-states-transboundary-particulate-matter-science-assessment-2013), ~90% of Canadians live within ~100 miles of the US border (https://www.cbc.ca/news/canada/by-the-numbers-1.801937), and ambient $PM_{2.5}$ concentrations are similar in Canada and the US. Additionally, this endpoint is more related to health physiology then healthcare systems and Canada and the US have similar prevalence rates of asthma (https://ourworldindata.org/grapher/asthma-prevalence).

administrative databases collectively known as Quebec Integrated Chronic Disease Surveillance System (QICDSS) between April 1, 1996 and March 31, 2011. The study defined the onset of asthma as a hospital discharged diagnosis of asthma or two reports of asthma from two separate physicians within a two-year period. The authors used Cox proportional hazard models to estimate the association between asthma onset and pollution exposure, controlling for demographics and socioeconomic status. Time-varying exposure models assessed time-varying exposures to the three pollutants in question. Tetreault et al., 2016 showed that childhood asthma onset may be associated with exposure to $PM_{2.5}$, NO_2, and O_3.

The identified study presented 24 hazard ratios using various adjustment methods and included multiple sensitivity analyses, evaluating the effects by sex, urbanicity, and those who moved during the study period. More-adjusted risk estimates using a time-varying estimate of $PM_{2.5}$ exposure and including the full cohort were identified over less-adjusted or striated estimates using exposure estimates at birth. The study identified as best characterizing risk across the U.S. was Tetreault et al., 2016, although the two older and demographic-limited U.S. studies were also identified as potentially informative.

The risk estimate identified from Tetreault et al., 2016 for use in the main benefits estimates was a single-pollutant time-varying hazard ratio model of 1.33 (95% CI: 1.31-1.34) for a 6.53 $\mu g/m^3$ (interquartile range) increase in annual $PM_{2.5}$ concentration at the residential address.

As the physiology and etiology of lung development in children is similar in children 6-17, we apply the 4-12 year age-striated effect estimate from Tetreault et al., 2016 to children ages 4-17 (Baena-Cagnani et al., 2007, Guerra et al., 2004, Ochs et al., 2004, Sparrow et al., 1991, Trivedi and Denton, 2019).

2.2.5.10 Asthma Symptoms/Exacerbation

The 2019 PM ISA stated that "evidence for effects on asthma exacerbation are generally more consistent than associations for other respiratory outcomes." The ISA went on to note that "recent studies strengthen the relationship between asthma exacerbation in children and short-term $PM_{2.5}$ exposure, while, in adults, the relationship continues to be inconsistent."

2.2.5.10.1 Available Epidemiologic Literature

Based on evidence provided by the 2019 PM ISA, available studies of asthma symptoms were limited to children, of which there were eight.

2.2.5.10.2 Identifying Suitable Studies for Use in Benefits Assessments

Due to the specificity required when evaluating this health endpoint, Individual studies of asthma exacerbation/symptoms tended to focus on relatively small cohorts of children of discrete ages in distinct locations, making pooling difficult. One study evaluated a directly monetizable outcome of albuterol inhaler use. Albuterol inhalers are separated from long-term asthma control medications and is considered a "rescue medication" by the Mayo Clinic, making it an informative endpoint when considering asthma symptoms.[49]

2.2.5.10.3 Studies and Risk Estimates Identified as Most Suitable for Use in Benefits Assessments

Rabinovitch et al., 2006 analyzed the relationship between short-term $PM_{2.5}$ exposure and asthma exacerbation in children. The study followed children, ages 6 to 13 attending the Kunsberg School at the

[49] https://www.mayoclinic.org/diseases-conditions/asthma/in-depth/asthma-medications/art-20045557

National Jewish Medical Research Center with diagnosed asthma for two consecutive winters from 2001-2003. Authors gave an electronic bronchodilator (albuterol) to the children to capture the frequency of use within a 24-hour period. The children also responded to three questions to determine if they may have an upper respiratory infection (URI), and urine samples were taken to measure urinary leukotriene E_4 levels on select days. The authors collected hourly ambient $PM_{2.5}$ levels from the Colorado Department of Health Air Pollution Control Division's Tapered Element Oscillating Microbalance (TEOM) monitor, located 2.7 miles west of the school. Additionally, a Federal Reference Monitor (FRM) located next to the TEOM measured 24-hour $PM_{2.5}$ levels. The authors obtained meteorological data from the Colorado Department of Health Air Pollution Control Division and the National Climatic Data Center. A Poisson regression modeled albuterol use as a function of the morning (12:00am to 11:00 am) maximum hourly $PM_{2.5}$ level or the morning mean hourly $PM_{2.5}$ level. The model used both the TEOM and FRM data, individually, incorporated four lag periods (0 to 2 days and 0- to 2-day average), and included several covariates: temperature, pressure, humidity, time trend, Friday indicator, and URI indicator. Rabinovitch et al., 2006 found that, although the $PM_{2.5}$ pollution levels were well below the National Ambient Air Quality Standards, there is a consistent association between peak ambient $PM_{2.5}$ levels and increased albuterol use in asthmatic children. The identified percent of use increase estimate of 1.2% (95% CI: -0.6-2.9) for a 6 $\mu g/m^3$ increase in averaged daily mean $PM_{2.5}$ concentration lagged by 0-, 1-, and 2-days came from a single-pollutant model.

2.2.5.11 Allergic Rhinitis (Hay Fever/Respiratory Allergies))

The 2019 $PM_{2.5}$ ISA stated that "recent studies evaluated associations between long-term exposure to $PM_{2.5}$ and various allergic outcomes in a mix of large representative cohort and cross-sectional survey studies" finding "generally consistent evidence of an association between long-term $PM_{2.5}$ exposure and allergic sensitization in single pollutant models" ((U.S. EPA, 2020a, section 5.2.4). Additionally, the ISA called out "allergic responses" in the biological plausibility diagram for long-term $PM_{2.5}$-attributable respiratory effects (U.S. EPA, 2020a, section 2.2.1.2.1.2). Although cross sectional analyses do not establish a temporal sequence, they can be used to estimate benefits associated with changes in air quality.

2.2.5.11.1 Available Epidemiologic Literature

The 2019 PM ISA identified one epidemiologic study of long-term 2019 $PM_{2.5}$ exposure and allergic rhinitis.

2.2.5.11.2 Studies and Risk Estimates Identified as Most Suitable for Use in Benefits Assessments

Parker et al., 2009 investigated the associations between long-term $PM_{2.5}$ exposure and respiratory allergies in an unrestricted population of children (aged 3-17 years) sampled from the United States National Health Interview Survey. Authors obtained symptom data from participant parents, who reported respiratory allergies on annual surveys. Parker et al., 2009 placed all study participants reporting symptoms of respiratory allergies or hay fever into a combined rhinitis group. Parker et al., 2009 then linked annual averages of SO_2, NO_2, $PM_{2.5}$, and $PM_{2.5-10}$ and warm season (May to September) O_3 averages to participant's addresses through ambient air pollution and meteorological data (O_3, SO_2, NO_2, $PM_{2.5}$, and $PM_{10-2.5}$) collected from US EPA Air Quality System monitors. The authors adjusted models for survey year, poverty-level, race/ethnicity, age, family structure, insurance coverage, usual source of care, education of adult, urban-rural status, region, and median county-level income. Through

multi-pollutant, logistic regression models, an odds ratio of 1.29 (95% CI: 1.07-1.56) for a 10 μg/m^3 increase in $PM_{2.5}$ concentrations and respiratory allergies was identified.

2.2.5.12 Minor Restricted Activity Days

No new epidemiologic studies of minor restricted activity days (MRADs) were identified in the 2019 PM ISA (U.S. EPA, 2019c).

2.2.5.12.1 Studies and Risk Estimates Identified as Most Suitable for Use in Benefits Assessments

Ostro and Rothschild, 1989 estimated the impact of $PM_{2.5}$ and O_3 on the incidence of minor restricted activity days (MRADs) and respiratory-related restricted activity days (RRADs) in a national sample of the adult working population, ages 18 to 65, living in metropolitan areas. The study population is based on the Health Interview Survey (HIS), conducted by the National Center for Health Statistics. In publications from this ongoing survey, non-elderly adult populations are generally reported as ages 18-64. From the study, it is not clear if the age range stops at or includes those aged 65. We apply the risk estimate function to individuals ages 18-64 for consistency with other studies estimating impacts to non-elderly adult populations. The annual national survey results used in this analysis were conducted in the period 1976-1981, controlling for $PM_{2.5}$, two-week average O_3.

2.2.5.13 Work Loss Days

No new studies of work loss days (WLDs) were identified in the 2019 PM ISA (U.S. EPA, 2019c).

2.2.5.13.1 Studies and Risk Estimates Identified as Most Suitable for Use in Benefits Assessments

Ostro, 1987 estimated the impact of PM2.5 on the incidence of work-loss days (WLDs), restricted activity days (RADs), and respiratory-related RADs (RRADs) in a national sample of the adult working population, ages 18 to 65, living in metropolitan areas. The study population is based on the Health Interview Survey (HIS), conducted by the National Center for Health Statistics. The annual national survey results used in this analysis were conducted in 1976-1981. Ostro, 1987 reported that two-week average PM2.5 levels were significantly linked to work-loss days, RADs, and RRADs, however there was some year-to-year variability in the results. Separate coefficients were developed for each year in the analysis (1976-1981); these coefficients were pooled. The coefficient used in the concentration-response function presented here is a weighted average of the coefficients in Ostro, 1987, Table III, using the inverse of the variance as the weight.

2.2.5.14 Lung Cancer

The 2019 PM ISA determined that a "likely to be causal" relationship exists between long-term $PM_{2.5}$ exposure and cancer (U.S. EPA, 2019c), a change in the causality determination from the 2009 ISA (U.S. EPA, 2009). Specifically, the ISA found evidence of generally consistent positive associations between long-term $PM_{2.5}$ exposure and lung cancer incidence.[50] Additional details regarding potential pathways of disease development are summarized in the biological plausibility diagram provided by the ISA (section 2.2.1.2.1.3).

For an outcome such as lung cancer, there is an expected time lag between changes in pollutant exposure in a given year and the reduction in lung cancer incidence, known as the latency period. The

[50] The ISA also found generally consistent positive associations between long-term $PM_{2.5}$ exposure and lung cancer mortality, but as mortality impacts are included elsewhere (section 2.2.5.1), this endpoint focuses on non-fatal lung cancer incidence.

time between exposure and diagnosis can be quite long, on the order of years to decades. We discuss methods used to account for the latency period and other economic considerations relevant to this health endpoint in section 5.3.6. Importantly, we include this health endpoint to assess impacts of living with a lung cancer diagnosis, prior to disease resolution or death.

2.2.5.14.1 Available Epidemiologic Literature

We limited our pool of available studies to those of lung cancer incidence, excluding those assessing lung cancer mortality as that endpoint is included in the long-term exposure-attributable all-cause mortality endpoint (section 2.2.5.1.3.1). This resulted in four study options.

2.2.5.14.2 Identifying Suitable Studies for Use in Benefits Assessments

The four available studies varied in terms of population demographics included and country. Two of the four studies took place entirely in Canada. Of the two U.S.-based studies, one included all ages, sexes, and demographics and was restricted to non- and never-smokers, although it included some participants living in Canada. The identified study was most suitable as it took place in the U.S., included both males and females, and was restricted to non- and never-smokers (Gharibvand et al., 2017).

2.2.5.14.3 Studies and Risk Estimates Identified as Most Suitable for Use in Benefits Assessments

Gharibvand et al., 2017 evaluated whether positive associations exist between $PM_{2.5}$ exposure and incidence of lung cancer in non-smokers among the Adventist Health and Smog Study-2 (AHSMOG-2), a group of health-conscious individuals of which 81% are never smokers. Authors collected ambient air pollution data ($PM_{2.5}$ and O_3) from the US EPA Air Quality system over two years (January 2000-December 2001). Three *a priori* factors were added to the models as covariates: time spent outdoors, residence length, and moving distance during follow-up. Authors modeled the association between $PM_{2.5}$ exposure and incidence of lung cancer using a Cox proportional hazards regression, with attained age as the time variable. The authors conducted both a single and a two-pollutant ($PM_{2.5}$ and O_3) analyses. The study concluded that each 10 $\mu g/m^3$ increase in ambient $PM_{2.5}$ concentrations was positively associated with increased lung cancer risks within the single-pollutant and two-pollutant multivariable models with O_3. The identified hazard ratio of 1.46 (95% CI: 1.13-1.89) for each 10 $\mu g/m^3$ increase in mean monthly ambient $PM_{2.5}$ concentrations came from a two-pollutant multivariable model with O_3 (including *a priori* covariates).

2.2.5.15 Alzheimer's Disease

Evidence connecting long-term $PM_{2.5}$ exposure to nervous system effects led to the 2019 ISA concluding a "likely to be causal" relationship exists (U.S. EPA, 2019c) and various clinically relevant nervous system endpoints were called out in the biological plausibility section, including Alzheimer's disease, Parkinson's disease, autism spectral disorder, cognitive decline, and dementia (section 2.2.1.2.1.3). Regarding biological plausibility, the ISA stated that "neuroinflammation and neurodegeneration provide biological plausibility for epidemiologic results of increased hospital admissions or emergency department visits for Alzheimer's and Parkinson's disease."

There were over a dozen epidemiologic studies in the 2019 PM ISA evaluating cognitive-related outcomes (U.S. EPA, 2019c, sections 8.2.5-8.2.7). However, due to the nature of the endpoint, many of the outcomes were defined using scales and scores from cognitive tests. As we are currently unable to transfer that type of result into a clinically relevant population level outcome, we focused on the more clearly defined outcomes of Alzheimer's disease and Parkinson's Disease. These endpoints were also

specifically called out in the ISA, as "epidemiologic studies also provide evidence of cognitive impairment and Alzheimer's and Parkinson's disease in association with exposure to $PM_{2.5}$" ((U.S. EPA, 2019c, section 8.2.6).

2.2.5.15.1 Available Epidemiologic Literature

One epidemiologic study of Alzheimer's disease met our minimum required identification criteria (section 2.1.1).

2.2.5.15.2 Studies and Risk Estimates Identified as Most Suitable for Use in Benefits Assessments

Kioumourtzoglou et al., 2016 evaluated the potential impact of long-term $PM_{2.5}$ exposure on first hospital admission for dementia, Alzheimer's, or Parkinson's diseases among Medicare beneficiaries (>= 65 years old) in 50 cities in the northeastern U.S. (Connecticut, Delaware, Maine, Maryland, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont, and Washington, D.C.). Authors retrieved medical data from the Center for Medicaid and Medicare from the years 1999-2010. The study followed enrollees as a cohort, which included annual follow-up records identifying the first hospital admissions for dementia (ICD-9 290), Alzheimer's (ICD-9 331.0), Parkinson's (ICD-9 332), and other cardiovascular comorbidities. With respect to Alzheimer's disease, the study evaluated 9,817,806 Medicare enrollees and included 266,725 cause-specific hospital admissions indicating disease onset. Annual average $PM_{2.5}$ concentrations were estimated for each city using data from the U.S. EPA Air Quality System database. Kioumourtzoglou et al., 2016 fit a time-varying Cox proportional hazards model for each city, using the city-wide annual $PM_{2.5}$ concentrations as the time-varying exposure of interest and a linear term for the calendar year. This eliminated the impact of $PM_{2.5}$ variation by city and any $PM_{2.5}$ trends within cities. The model adjusted for cardiovascular comorbidities, and incorporated a counting process extension which created an observation for each year of follow-up per person. The results were then pooled across individuals and cities. A single-pollutant model was used to develop the identified hazard ratio of 1.15 (95% CI: 1.11-1.19) for a 1 $\mu g/m^3$ increase in the average annual $PM_{2.5}$ concentrations.

2.2.5.16 Parkinson's Disease

Evidence connecting long-term $PM_{2.5}$ exposure to nervous system effects led to the 2019 ISA concluding a "likely to be causal" relation exists (U.S. EPA, 2019c) and various clinically relevant nervous system endpoints were called out in the biological plausibility section, including Alzheimer's disease, Parkinson's disease, autism spectral disorder, cognitive decline, and dementia (section 2.2.1.2.1.3). Regarding biological plausibility, the ISA stated that "neuroinflammation and neurodegeneration provide biological plausibility for epidemiologic results of increased hospital admissions or emergency department visits for Alzheimer's and Parkinson's disease."

There were over a dozen epidemiologic studies in the 2019 PM ISA evaluating cognitive-related outcomes (U.S. EPA, 2019c, sections 8.2.5-8.2.7). However, due to the nature of the endpoint, many of the outcomes were defined using scales and scores from cognitive tests. As we are currently unable to transfer that type of result into a clinically relevant disease incidence, we focused on the more clearly defined outcomes of Alzheimer's disease and Parkinson's Disease. These endpoints were also specifically called out in the ISA, as "epidemiologic studies also provide evidence of cognitive impairment and Alzheimer's and Parkinson's disease in association with exposure to $PM_{2.5}$" ((U.S. EPA, 2019c, section 8.2.6).

2.2.5.16.1 Available Epidemiologic Literature

Three epidemiologic studies of Parkinson's disease were identified in the 2019 PM ISA. All evaluated relatively low $PM_{2.5}$ concentrations and included participants from multiple states, however there were differences with respect to the ages and sexes evaluated, number of overall participants, and exposure estimation technique.

2.2.5.16.2 Identifying Suitable Studies for Use in Benefits Assessments

The prospective study with the lowest mean $PM_{2.5}$ concentrations and most recent timespan included over 14 times the number of participants as the other two studies combined. It was also the only study to include participants over the age of 71, which is relevant as Parkinson's disease prevalence rises with age (Pringsheim et al., 2014).

2.2.5.16.3 Studies and Risk Estimates Identified as Most Suitable for Use in Benefits Assessments

Kioumourtzoglou et al., 2016 evaluated the potential impact of long-term $PM_{2.5}$ exposure on first hospital admission for dementia, Alzheimer's, or Parkinson's diseases among Medicare beneficiaries (>= 65 years old) in 50 cities in the northeastern U.S. (Connecticut, Delaware, Maine, Maryland, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont, and Washington, D.C.). Authors retrieved medical data from the Center for Medicaid and Medicare from the years 1999-2010. The study followed enrollees as a cohort, which included annual follow-up records identifying the first hospital admissions for dementia (ICD-9 290), Alzheimer's (ICD-9 331.0), Parkinson's (ICD-9 332), and other cardiovascular comorbidities. With respect to Parkinson's disease, the study evaluated 9,817,806 Medicare enrollees and included 119,425 cause-specific hospital admissions indicating disease onset. Annual average $PM_{2.5}$ concentrations were estimated for each city using data from the US EPA Air Quality System database. Kioumourtzoglou et al., 2016 fit a time-varying Cox proportional hazards model for each city, using the city-wide annual $PM_{2.5}$ concentrations as the time-varying exposure of interest and a linear term for the calendar year. This eliminated the impact of $PM_{2.5}$ variation by city and any $PM_{2.5}$ trends within cities. The model adjusted for cardiovascular comorbidities, and incorporated a counting process extension which created an observation for each year of follow-up per person. The results were then pooled across individuals and cities. A single-pollutant model was used to develop the identified hazard ratio of 1.08 (1.04 – 1.12) for a 1 $\mu g/m^3$ increase in the average annual $PM_{2.5}$ concentrations.

2.2.6 O_3

The following sections of the 2020 O_3 ISA correspond to health endpoints judged as having a "causal" or "likely causal" relationship with O_3 exposure:

- Appendix 3: Health Effects – Respiratory, 3.1 Short-Term Ozone Exposure;
- Appendix 3: Health Effects – Respiratory, 3.2 Long-Term Ozone Exposure;
- Appendix 5: Health Effects – Metabolic Effects, 5.1 Short-Term Ozone Exposure;
- Appendix 6: Health Effects – Mortality, 6.1 Short-Term Ozone Exposure and Mortality; and
- Appendix 6: Health Effects – Mortality, 6.2 Long-Term Ozone Exposure and Mortality.

Following the approach to identifying available epidemiologic literature (section 2.2), we began with the 1,678 studies cited by the 2020 O_3 ISA. Of these, 130 morbidity studies evaluate health endpoints the 2020 O_3 ISA determined as having a "causal" or "likely causal" relationship with O_3 exposure (sections 2.2.1 and 2.2.2). 77 studies remained after the required minimum criteria were applied, and that

number decreased to 27 when broad hospital admissions and emergency department endpoints were identified.[51] No studies of short-term O_3 exposure metabolic effects meeting the minimum required criteria (section 2.1.1) were identified in the ISA.

Table 7. O_3 Study and Risk Estimate Identification Diagram

O_3 Endpoint and Exposure Duration	Studies Available	Studies Included	Ages	Risk Estimates Available	Risk Estimates Included
Respiratory Mortality (LT)	4	1	Adults and older adults	2	1
Respiratory Mortality (ST)	6	2	Children, adults, and older adults	16	1
				120	1
Respiratory Hospital Admissions (ST)	3	1	Older adults	7	1
Respiratory Emergency Department Visits (ST)	7	1	Children, adults, and older adults	45	5
Asthma Onset (LT)	4	1	Children	8	1
Asthma Symptoms (ST)	4	1	Children	160	1
Minor Restricted Activity Days	NA	1	Adults	NA	1
Allergic Rhinitis	1	1	Children	5	1
School Loss Days	NA	2	Children	NA	1
				NA	1

NA- not applicable due to the absence of additional ISA evidence. Risk estimates identified in the 2015 Ozone NAAQS RIA will continue to be utilized.

2.2.6.1 Respiratory Mortality

We separate respiratory mortality impacts resulting from short- and long-term exposures for several reasons. Firstly, the biological pathways of short- and long-term O_3-attributable health effects may differ in ways that affect the manner in which this endpoint is quantified (section 2.2.1.2.2.1). For example, some impacts of long-term exposure to O_3 may be incremental to impacts attributable to short-term exposure. Conversely, some impacts associated with long-term exposure to O_3 may include impacts attributable to short-term exposure. However, we lack the evidence to determine the extent to which these risks are mutually exclusive or overlapping. Secondly, the level of support for respiratory mortality effects of short- and long-term O_3 exposures may differ. Therefore, we continue to include risk estimates of respiratory mortality from both short- and long-term exposures to present a range of health impact estimates.

2.2.6.1.1 Respiratory Mortality Attributable to Short-Term Exposures

The 2020 O_3 ISA determined that there exists a "causal" relationship between short-term O_3 exposure and respiratory outcomes (U.S. EPA, 2020a). The short-term exposure causality determination "was made on the basis of a strong body of evidence integrated across controlled human exposure, animal toxicological, and epidemiologic studies, in addition to established findings from previous [Air Quality

[51] This number may not be equal to the sum of available studies in Table 7 as individual studies may present risk estimates for multiple health endpoints.

Criteria Documents], demonstrating respiratory effects due to short-term exposure to ozone." While the ISA found that "recent epidemiological evidence for respiratory mortality is limited, but there remains evidence of consistent, positive associations, specifically in the summer months" and "when recent evidence is considered in the context of the larger number of studies evaluated in the 2013 Ozone ISA, there remains consistent evidence of an association between short-term ozone exposure and respiratory mortality." Due to the strength of the ISA evidence relating short-term exposures to respiratory mortality, estimates of respiratory mortality impacts are included in the main benefits assessment of O_3-attributable health impacts.

Separately, 2020 ISA determined that the relationship between short-term O_3 exposure and total mortality is "suggestive of, but not sufficient to infer, a causal relationship." By comparison, the 2013 ISA identified this endpoint as "likely to be causal." Evidence supporting a relationship between short-term O_3 exposure and total mortality included consistent epidemiologic evidence from multiple high-quality studies at relevant ozone concentrations, some support for an independent O_3 association, and biological plausibility from studies of respiratory morbidity. In contrast, uncertainties remain regarding geographic heterogeneity in O_3 mortality associations and there is limited biological plausibility from studies of cardiovascular morbidity. Regarding the biological plausibility of cardiovascular effects, while animal toxicological studies provide evidence of cardiovascular effects, recent controlled human exposure studies do not provide evidence to support potential biological pathways. Additionally, there is a lack of coherence with epidemiologic studies of cardiovascular morbidity, specifically, cardiovascular-related emergency department visits and hospital admissions, to support cardiovascular mortality. Due to limitations in ISA evidence relating short-term exposures to total mortality, estimates of all-cause mortality impacts will not be calculated when estimating benefits attributable to changes in O_3 exposure.

2.2.6.1.1.1 Available Epidemiologic Literature

There were six North American studies of short-term O_3-attributable respiratory mortality identified in the 2020 O_3 ISA, one of which was new to this review but took place entirely in Canada. Of the U.S.-based studies, two were single-city. The other three studies were fairly equally geographically and demographically representative, although one was a meta-analysis.

2.2.6.1.1.2 Identifying Suitable Studies for Use in Benefits Assessments

Of the six studies of short-term O_3-attributable respiratory mortality, all but one study period ended during or before the year 2000 and the individual study that extended into the 2000s was geographically limited to a single city. This list also included a meta-analysis and a study that took place entirely in Canada. Two U.S.-based, nationally representative studies were identified as best characterizing risk across the U.S. for this endpoint.

2.2.6.1.1.3 Studies and Risk Estimates Identified as Most Suitable for Use in Benefits Assessments

As Zanobetti and Schwartz, 2008 investigated the effects of short-term O_3 exposure on mortality (all-cause, cardiovascular, stroke, and respiratory) in an unrestricted population of children, adults, and older adults (aged 0-99 years), it remained the superior analysis of short-term O_3-attributable respiratory mortality. Between 1998 and 2000, the authors collected mortality data from the National Center for Health Statistic in 48 cities across the United States. Along with eight-hour ozone concentrations and meteorological data obtained from US EPA's Air Quality System Technology Transfer Network, the authors utilized a generalized linear model with quasi Poisson link functions to estimate

the effects of short-term ozone on respiratory mortality. The model adjusted for season, day of the week, and temperature. Since ozone concentrations vary between seasons, the authors decided to restrict their analysis to ozone warm season (June - August). The identified single-pollutant, warm season excess risk estimate of 0.83% (95% CI: 0.38-1.28%) for an increase of 10 ppb in DA8 O_3 concentrations over a summed lag structure of zero to three days.

Katsouyanni et al., 2009 also used time series methods to examine the relationship between short-term O_3 exposures and mortality across the U.S for all ages. The study utilized mortality data from the National Center for Health Statistics (www.cdc.gov/nchs) for years 1987 through 1996, excluding accidental deaths (i.e., International Classification of Diseases (ICD]-9 800). 90 U.S. cities with population sizes varying from about 250,000 to above 9 million with the largest populations were included. Daily number of deaths ranged from 5 to 198. All 90 cities had daily summer O_3 measurements. Investigators conducted extensive simulation studies to test 1) the choice of the smoothing method and basic functions used to estimate the smooth function of time in the city-specific models, and 2) the number of degrees of freedom to be used in the smooth function of time. The investigators also evaluated whether each city should be assigned the same model specification or whether each city-specific model should depend on city-specific characteristics. For the former, the same degrees of freedom (ranging from 1 to 20 df/year of data) were assigned to the smooth function of time for every city. The range was determined by choosing the minimum possible degrees of freedom per year up to a maximum degrees of freedom per year that essentially removed all variation in the data beyond time scales of one week. Also, the collective experience of the investigators indicated that using more than 20 df/year does not substantially affect the risk estimates. For the latter approach, the degrees of freedom for the smooth function of time were chosen separately for each city using a fit criterion, such as the Akaike Information Criterion (AIC), or by minimizing the partial autocorrelation function (PACF) of the residuals. Nonparametric methods underestimated the standard error of the air pollution regression coefficient, penalized splines gave relatively small bias, and PACF in combination with penalized splines performed relatively well in terms of bias. Therefore, the identified risk estimate was a summer-only penalized spline estimate of respiratory mortality of 0.73 (-0.39, 1.85) per 10 $\mu g/m^3$ increase in O_3 from distributed lag days was identified.

The two risk estimates identified are not directly comparable to previous estimates of short-term exposure-related mortality as previous estimates were of nonaccidental mortality and current estimates are of respiratory mortality.

2.2.6.1.2 Respiratory Mortality Attributable to Long-Term Exposures

The 2020 O_3 ISA determined that there exists a “likely to be causal” relationship between long-term O_3 exposure and respiratory outcomes ({U.S. EPA, 2020 #343. The overall “likely to be causal” determination for long-term exposures “was based on epidemiologic evidence of associations between long-term ozone exposure and asthma development, respiratory symptoms in children with asthma, and respiratory mortality.” More specifically, the ISA found that “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” and the “several multicity studies and a multi-continent study reported associations between short-term increases in ozone concentrations and increases in respiratory mortality.” Overall, the 2020 O_3 ISA concluded there was “some evidence that long-term

ozone exposure is associated with respiratory mortality, but the evidence is not consistent across studies." Due to the strength of the ISA evidence relating long-term exposures to respiratory mortality, estimates of respiratory mortality impacts are included when estimating benefits attributable to changes in O_3 exposure.

2.2.6.1.2.1 Available Epidemiologic Literature

There were four North American studies of long-term O_3-attributable respiratory mortality identified in the 2020 O_3 ISA, three of which were new to this review.[52] All four studies evaluated either the ACS CSP-II or the Canadian Census Health and Environment Cohort (CanCHEC) prospective cohorts, differing in study size, timespan, exposure estimation technique, and specific risk models analyzed.

2.2.6.1.2.2 Identifying Suitable Studies for Use in Benefits Assessments

Three of the four studies evaluating long-term O_3-attributable respiratory mortality assessed the ACS CSP-II prospective cohort and the fourth evaluated the Canadian Census Health and Environment Cohort (CanCHEC) prospective cohort. Two of the three ACS CSP-II analyses were nationwide, with the third focusing on California. One of the two nationwide ACS CSP-II analyses included a longer and more recent study period, utilized hybrid exposure estimates, and included a larger number of participants.

2.2.6.1.2.3 Studies and Risk Estimates Identified as Most Suitable for Use in Benefits Assessments

{Turner, 2016 #544} examined the relationship between long-term O_3 exposure (1982-2004) and mortality (all-cause, cause-specific) in American Cancer Society Cancer Prevention Study-II participants (aged 30-99 years). A hierarchal Bayesian space-time model based on National Air Monitoring Stations, State and Local Air Monitoring Stations, and Community Multi-Scale Air Quality model data estimated daily eight-hour maximum ozone concentrations at the participant's address. The models considered meteorological data and levels of other ambient pollutants ($PM_{2.5}$, both regional and near-source, and NO_2). Turner et al., 2016 utilized Cox proportional hazard models adjusted *a priori* for individual, socio-demographic, and ecological variables. The hazard ratio of 1.12 (1.08 – 1.16) from a multi-pollutant, all-year model of respiratory mortality for a 10 ppb increase in the annual average of daily 8-hour maximum ozone concentrations was likely the most comprehensive risk estimate. This study also provided a warm-season specific hazard ratio of 1.08 (1.06-1.11) per 10 ppb increase in seasonal average of daily 8-hour maximum O_3 concentrations, which will be used when air quality surfaces are only available for the summer season. Notably, the study compared annual mortality with warm-season O_3 exposures, so full-year baseline incidence rates will be used with risk estimates from this study.

The identified risk estimate of long-term exposure associated mortality is larger than the risk estimate used in previous benefits assessments (Jerrett et al., 2009), but differs in many aspects including study size, included study locations, and exposure estimation technique.

2.2.6.2 Respiratory Hospital Admissions

After considering the relationships between specific and broad respiratory hospital admission endpoints, the 2020 O_3 ISA stated that "studies conducted in diverse locations with a variety of exposure assignment techniques continue to provide evidence of an association between ozone and both hospital

[52]The 2020 O_3 ISA identified five North American studies of long-term O_3-attributable respiratory mortality, but as Weichenthal et al., 2016 examined the combined oxidant capacity of O_3 and NO_2, and not direct effects of O_3 alone, it did not meet required minimum criteria for consideration for inclusion in benefits assessments (section 2.1.1).

admissions and emergency department visits for combined respiratory diseases" (U.S. EPA, 2020a, section 3.1.8).

2.2.6.2.1 Available Epidemiologic Literature

Three epidemiologic studies of respiratory hospital admission were identified in the 2020 O_3 ISA, which varied considerably with respect to the timespans evaluated and study population locations (U.S. EPA, 2020a).

2.2.6.2.2 Identifying Suitable Studies for Use in Benefits Assessments

The two older studies either included only Canadian participants or included U.S., Canadian, and some European participants. Therefore, we identified the most recent and only entirely U.S.-based study as best characterizing risk across the U.S.

2.2.6.2.3 Studies and Risk Estimates Identified as Most Suitable for Use in Benefits Assessments

Katsouyanni et al., 2009 used time series methods to examine the relationship between daily O_3 concentrations and hospital admissions in North America. For U.S. benefits estimation purposes, we focus on analyses performed using the U.S hospital admission datasets. These datasets included 14 cities with populations between 291,000 and 5,377,000 between 1987-1996 with city-wide MDA1 O_3 concentrations ranging from ~34-60 μg/m^3. The authors used a first stage analysis protocol that used generalized linear models with either penalized or natural splines to adjust for seasonality, with varying degrees of freedom. The number of degrees of freedom were also chosen by minimizing the partial autocorrelation function of the model's residuals. Model specification approach accounted for seasonal patterns, weekend and vacation effects, and epistemics of respiratory disease. Data were also analyzed to detect potential thresholds in the concentration-response relationships. The second stage analysis used pooling approaches and assessed potential effect modification by sociodemographic characteristic and indicators of the pollution mixture across study regions. The identified percent change in respiratory disease admission for those aged >64 was from a copollutant model including PM_{10} is 0.28 (-0.07, 0.62) per 10 μg/m^3 increase in O_3.

2.2.6.3 Respiratory Emergency Department Visits

After considering the relationships between specific and broad respiratory emergency department visit endpoints, the 2020 O_3 ISA stated that "studies conducted in diverse locations with a variety of exposure assignment techniques continue to provide evidence of an association between ozone and both hospital admissions and emergency department visits for combined respiratory diseases" and "there is some evidence, previously characterized in the 2013 O_3 ISA, that daily 8 hour max, 1 hour max, and daytime average O_3 concentrations may be most strongly associated with respiratory emergency department visits" (U.S. EPA, 2020a, section 3.1.8).

2.2.6.3.1 Available Epidemiologic Literature

Seven U.S.-based studies of respiratory emergency department visits were identified in the 2020 O_3 ISA (U.S. EPA, 2020a). As is common with hospital admission and emergency department health endpoints, the specific ICD codes varied across all studies, making pooling difficult. Most studies evaluated only a single city or state and took place in a similar time period, including the early 2000s.

2.2.6.3.2 Identifying Suitable Studies for Use in Benefits Assessments

Available studies varied most widely by geographic area, exposure estimation method, population age range, and O_3 season. While most studies focused on a specific city, state or region, one study included five different multi-county areas. In addition, it included a recent time period, all ages, current O_3 concentrations, and was one of only two studies based on hybrid exposure techniques.

2.2.6.3.3 Studies and Risk Estimates Identified as Most Suitable for Use in Benefits Assessments

Barry et al. (2018) investigated the effects of short-term ozone exposure on emergency department visits for respiratory disease (ICD-9 493, 786.07, 460-466, 477, 491, 492, 496, 480–486, 466.1, 466.11, 466.19) in an unrestricted population of children, adults, and older adults (aged zero-99 years) within five cities (Atlanta, GA, Birmingham, AL, Dallas, TX, Pittsburgh, PA, and St. Louis, MO-IL) across the United States. Authors obtained individual-level health data from hospitals and hospital associations in each of the five cities. Models fusing air quality monitor data with Community Multi-Scale Air Quality modeled data at 12 x 12-km grids were used to estimate ozone exposure. Barry et al. (2018) assessed associations with short-term ozone exposure with daily eight-hour maximum ozone concentrations. The authors implemented Poisson log-linear models to estimate risk values with three day moving averages. They identified single-pollutant rate ratios of 1.03 (95% CI: 1.01-1.05) in Atlanta, GA, 1.03 (95% CI: 1.00-1.06) in Birmingham, AL, 1.05 (95% CI: 1.02-1.07) in Dallas TX, 1.03 (95% CI: 1.01-1.05) in Pittsburgh, PA, and 1.02 (95% CI: 1.01-1.04) in St. Louis, MO-IL for an increase of 25 ppb in full-year MDA8 O_3 concentrations (three day moving average). Results from individual cities are pooled.

2.2.6.4 Asthma Onset

The 2020 O_3 ISA concluded that "recent epidemiologic studies provide generally consistent evidence for associations of long-term ozone exposure with the development of asthma in children" (U.S. EPA, 2020a, section IS.4.3). The ISA also found that "recent animal toxicological studies demonstrate effects on airway development in rodents…and build on and expand the evidence for long-term ozone exposure-induced effects that may lead to asthma development" and asthma onset was called out as a key population level clinically relevant health endpoint in the biological plausibility pathways (section 2.2.1.2.2.1, Figure 9). More specifically, the O_3 ISA stated that a "limited number of recent epidemiologic studies provide generally consistent evidence that long-term ozone exposure is associated with the development of asthma in children" (U.S. EPA, 2020a, section 3.2.6).

2.2.6.4.1 Available Epidemiologic Literature

The 2020 O_3 ISA identified children as the population in which this health effect was observed, so we began with the four ISA-identified studies of people <21 (U.S. EPA, 2020a).

2.2.6.4.2 Identifying Suitable Studies for Use in Benefits Assessments

Three studies evaluated prospective cohorts, two of which included more recent timespans and likely lower O_3 concentrations. One of those studies took place entirely in Canada but included a substantially larger study size (>200 times larger) than the other. As the asthma onset endpoint is consistent between studies, pooling may be appropriate.

2.2.6.4.3 Studies and Risk Estimates Identified as Most Suitable for Use in Benefits Assessments

Tetreault et al., 2016 investigated the effects of long-term O_3 exposure on asthma onset in children (aged zero-12 years) from Québec, Canada. The study followed participants from the Québec Integrated Chronic Disease Surveillance System open birth cohort between 1999 and 2011. The authors defined

new cases of asthma based on hospital discharge reports and physician diagnoses (two diagnoses within a two-year span). Monitor data (Canadian National Air Pollution Surveillance network) and land-use mixed effect models estimated warm season (June to August) O_3 exposures. Authors assessed associations with asthma onset with both time of birth and time-varying exposure models and adjusted for year of birth, sex, and indices of social and material deprivation. Tetreault et al., 2016 used Cox proportional hazard models to observe associations between long-term O_3 exposure and asthma onset in children. The identified single-pollutant, warm-season hazard ratio was 1.07 (95% CI: 1.06-1.08) for a 3.26 ppb (interquartile range) increase in annual O_3 concentrations.

As the physiology and etiology of lung development in children is similar in children 6-17 (Baena-Cagnani et al., 2007, Guerra et al., 2004, Ochs et al., 2004, Sparrow et al., 1991, Trivedi and Denton, 2019), we apply the 4-12 year age-stratified effect estimate from Tetreault et al., 2016 to children ages 4-17.

2.2.6.5 Asthma Symptoms

Asthma symptoms/exacerbation is identified as a health effect of short-term O_3 exposure (section 2.2.1.2.2.1). Overall, the ISA found that "evidence from recent epidemiologic and experimental studies continues to support an association between ozone and asthma exacerbation" with "associations…observed across a range of ozone concentrations, and…consistent in models with measured or modeled concentrations" (U.S. EPA, 2020a, section 3.1.5.7).

2.2.6.5.1 Available Epidemiologic Literature

Four epidemiologic studies of asthma symptoms meeting our minimum criteria (section 2.1.1) were identified in the 2020 O_3 ISA (U.S. EPA, 2020a). Most studies took place in the late nineties and very early 2000s, and although no study included >1000 participants, there was appreciable geographic representation. There were also differences regarding the ozone season. Only the oldest study specifically evaluated a warm season, although a more recent study did skew slightly toward warmer seasons, evaluating eight seasons over a four-year timespan (two Summers, three Springs, two Falls, and one Winter).

2.2.6.5.2 Identifying Suitable Studies for Use in Benefits Assessments

Two of the studies evaluated much higher O_3 concentrations (~50 ppb vs 30 ppb). Of the two studies evaluating lower pollutant concentrations, one employed a prospective study design and clearly defined the specific asthma symptoms evaluated (e.g., wheeze).

2.2.6.5.3 Studies and Risk Estimates Identified as Most Suitable for Use in Benefits Assessments

Lewis et al., 2013 studied the effects of short-term O_3 exposure on frequency of asthma symptoms in an asthmatic population of primarily lower-income, African American and Latino children (aged five-12 years) in East and Southwest Detroit, MI. Authors obtained health and demographic data through questionnaires filled out by parents or guardians for 14 consecutive days in each studied season. Questionnaires highlighted participant's asthma symptoms (cough, wheeze, shortness of breath, chest tightness), demographic information, medication use, and presence of second-hand smoke. The authors acquired maximum one-hour and maximum 8-hour O_3 concentrations and meteorological data from two community-level monitors placed on East and Southwest Detroit, MI school rooftops. Lewis et al., 2013 implemented a combination of generalized estimating equations and alternative logistic regression models to estimate the associations between short-term O_3 exposure and rate of asthma symptoms. Models adjusted for age, sex, location (Eastside or Southwest), race, household income, smoker in the

home, season, and variables for companion home intervention study (control or intervention), time (pre- or post-intervention), and the interaction between intervention group status and time. Lewis et al., 2013 observed positive associations between short-term O_3 exposure and asthma symptoms, including the identified single-pollutant, all year odds ratios of 1.12 (95% CI: 0.99-1.25) for cough, 1.13 (95% CI: 0.99-1.28) for wheeze, 1.20 (95% CI: 1.02-1.40) for chest tightness, and 1.07 (95% CI: 0.95-1.21) for shortness of breath, all for a 16 ppb (interquartile range) increase in 8-hour maximum O_3 concentrations (five-day average lag).[53]

2.2.6.6 Minor Restricted Activity Days

No new epidemiologic studies of minor restricted activity days (MRADs) were identified in the 2020 O_3 ISA (U.S. EPA, 2020a).

2.2.6.6.1 Studies and Risk Estimates Identified as Most Suitable for Use in Benefits Assessments

Ostro and Rothschild, 1989 estimated the impact of $PM_{2.5}$ and O_3 on the incidence of minor restricted activity days (MRADs) and respiratory-related restricted activity days (RRADs) in a national sample of the adult working population, ages 18 to 65, living in metropolitan areas. The study population is based on the Health Interview Survey (HIS), conducted by the National Center for Health Statistics. In publications from this ongoing survey, non-elderly adult populations are generally reported as ages 18-64. From the study, it is not clear if the age range stops at or includes those aged 65. We apply the risk estimate function to individuals ages 18-64 for consistency with other studies estimating impacts to non-elderly adult populations. The annual national survey results used in this analysis were conducted in the period 1976-1981, controlling for $PM_{2.5}$, two-week average O_3.

2.2.6.7 Allergic Rhinitis (Hay Fever/Respiratory Allergies))

The 2020 O_3 ISA stated that "cross-sectional epidemiologic studies provide generally consistent evidence that ozone concentrations are associated with hay fever/rhinitis" and included "allergic responses" in the biological plausibility diagram for long-term O_3-attributal respiratory effects (U.S. EPA, 2020a, section 2.2.1.2.2.1). Although cross sectional analyses do not establish a temporal sequence, they can be used to estimate benefits associated with changes in air quality.

2.2.6.7.1 Available Epidemiologic Literature

The 2020 O_3 ISA identified one epidemiologic study of long-term O_3 exposure and allergic rhinitis.

2.2.6.7.2 Studies and Risk Estimates Identified as Most Suitable for Use in Benefits Assessments

Parker et al., 2009 investigated the associations between long-term O_3 exposure and respiratory allergies in an unrestricted population of children (aged 3-17 years) sampled from the United States National Health Interview Survey. Authors obtained symptom data from participant parents, who reported respiratory allergies on annual surveys. Parker et al., 2009 placed all study participants reporting symptoms of respiratory allergies or hay fever into a combined rhinitis group. Parker et al., 2009 linked annual averages of SO_2, NO_2, $PM_{2.5}$, and $PM_{2.5-10}$ and warm season (May to September) O_3 averages to participant's addresses through ambient air pollution and meteorological data collected from US EPA Air Quality System monitors. The authors adjusted models for survey year, poverty-level, race/ethnicity, age, family structure, insurance coverage, usual source of care, education of adult, urban-rural status, region, and median county-level income. Through multi-pollutant, logistic regression

[53] Estimates were obtained from figures. Authors did not respond to requests for exact results.

models, the odds ratio of 1.18 (95% CI: 1.09-1.27) for a 10 ppb increase in 24-hour mean, warm season O_3 and respiratory allergies was identified.

2.2.6.8 School Loss Days

No new studies of work loss days (WLDs) were identified in the 2020 O_3 ISA (U.S. EPA, 2020a).

2.2.6.8.1 Studies and Risk Estimates Identified as Most Suitable for Use in Benefits Assessments

Gilliland et al., 2001 examined the association between air pollution and school absenteeism among fourth grade school children (aged nine to 10) in 12 southern Californian communities. The study was conducted from January through June 1996. The authors used school records to collect daily absence data and parental telephone interviews to identify causes. They defined illness- related absences as respiratory or non-respiratory. A respiratory illness was defined as an illness that included at least one of the following: runny nose/sneezing, sore throat, cough, earache, wheezing, or asthma attack. The authors used 15- and 30-day distributed lag models to quantify the association between O_3 and incident school absences. O_3 levels were positively associated with all school absence measures and significantly associated with all illness-related school absences (non-respiratory illness, respiratory illness, URI and LRI). The health impact function for ozone is based on the results of the single pollutant model.

Gilliland et al., 2001 defines an incident absence as an absence that followed attendance on the previous day and the incidence rate as the number of incident absences on a given day over the population at risk for an absence on a given day (i.e. those children who were not absent on the previous day). Since school absences due to air pollution may last longer than one day, an estimate of the average duration of school absences could be used to calculate the total avoided school loss days from an estimate of avoided new absences. A simple ratio of the total absence rate divided by the new absence rate would provide an estimate of the average duration of school absences, which could be applied to the estimate of avoided new absences as follows:

$$Duration = \frac{TotalAbsences}{NewAbsences}$$

$$\Delta TotalAbsences = -\left[incidences \times \left(e^{-\beta \times O_3} - 1\right)\right] \times duration \times pop$$

Since the function is log-linear, the baseline incidence rate (in this case, the rate of new absences) is multiplied by duration, which reduces to the total school absence rate. Therefore, the same result would be obtained by using a single estimate of the total school absence rate in the risk estimate. Using this approach, we assume that the same relationship observed between pollutant and new school absences in the study would be observed for total absences on a given day. As a result, the total school absence rate is used in the function below. The derivation of this rate is described in the section on baseline incidence rate estimation.

For all absences, the coefficient and standard error are based on a percent increase of 16.3 percent (95% CI -2.6 percent, 38.9 percent) associated with a 20 ppb increase in eight-hour average ozone concentration (2001, Table 6, p. 52).

A scaling factor is used to adjust for the number of school days in the ozone season. In the modeling program, the function is applied to every day in the ozone season (May 1 - September 30), however, in reality, school absences will be avoided only on school days. We assume that children are in school during weekdays for all of May, two weeks in June, one week in August, and all of September. This corresponds to approximately 2.75 months out of the five-month season, resulting in an estimate of 39.3% of days (2.75/5*5/7).

In addition, not all children are at-risk for a new school absence, as defined by the study. On average, 5.5% of school children are absent from school on a given day (NCES, 1996, Table 42-1). Only those who are in school on the previous day are at risk for a new absence (1-0.055 = 94.5%). As a result, a factor of 94.5% is used in the function to estimate the population of school children at-risk for a new absence.

2.3 IDENTIFIED STUDY AND RISK ESTIMATES FOR BENEFITS ASSESSMENTS

While we begin with studies identified in ISAs, the goals of an ISA differ greatly from those of benefits assessments. ISAs evaluate the overall state of the science and develop overarching conclusions relating exposure to health effects. This includes analyses of specific subgroups, such as people with pre-existing conditions, that may not be transferrable to the entire U.S. population.

In an effort to make our study and risk estimate identification process as transparent and reproducible as possible, we have explicitly stated the criteria used in our approach (section 1) as well as the available epidemiologic studies evaluated (section 2.2). However, even with such detailed information, expert judgment can be required if multiple estimates meet the required criteria, satisfy a similar number of preferred criteria, and are unable to be statistically aggregated into a single risk estimate (i.e., pooling).

The two tables in this section provide information on the health endpoints and risk estimates identified for use in $PM_{2.5}$ and O_3 benefits estimation (Table 10 and Table 11) using the systematic approach described above (sections 2.1 and 2.2).

2.3.1 Health Endpoints

These summary tables provided an overview of the $PM_{2.5}$ and O_3 health endpoints included in the main benefits analysis. They are the outcome of the systematic approach described above, which involved

consideration of recent ISA conclusions along with the availability of clinically relevant epidemiologic risk estimates (Table 8 and Table 9).

2.3.1.1 $PM_{2.5}$

Table 8. Set of Health Endpoints for Main $PM_{2.5}$ Benefits Assessments

Endpoint Group	Endpoint Type	Specific Endpoint	Exposure	Ages
Mortality	Mortality	All cause	LT	Adults and older adults (30-99 and 65-99 years)
			ST	Infants (1-12 months)
Cardiovascular Effects	Hospital Admissions	Cardiovascular Outcomes	ST	Older adults (65-99 years)
	Emergency Department Visits	Cardiovascular Outcomes	ST	Children, adults, and older adults (0-99 years)
	Incidence	Acute Myocardial Infarction	ST	Adults and older adults (18-99 years)
		Stroke[a]	LT	Older adults (65-99 years)
		Cardiac Arrest[a]	ST	Adults and older adults (0-99 years)
Respiratory Effects	Hospital Admissions	Respiratory Outcomes	ST	Children and older adults (65-99 years)
	Emergency Department Visits	Respiratory Outcomes	ST	Children, adults, and older adults (0-99 years)
	Incidence	Asthma Onset[a]	LT	Children (0-17 years)
		Asthma Symptoms	ST	Children (6-17 years)
		Allergic Rhinitis[a]	LT	Children (3-17 years)
		Minor Restricted Activity Days	NA	Adults and older adults (18-64 years)
		Work Loss Days	NA	Adults and older adults (18-64 years)
Cancer	Incidence	Lung Cancer[a]	LT	Adults and older adults (30-99 years)
Nervous System Effects	Hospital Admissions	Alzheimer's Disease[a]	LT	Older adults (65-99 years)
		Parkinson's Disease[a]	LT	Older adults (65-99 years)

[a]New health endpoint.

2.3.1.2 O_3

Table 9. Set of Health Endpoints for Main O_3 Benefits Assessments

Endpoint Group	Endpoint Type	Specific Endpoint	Exposure	Ages
Mortality	Mortality	Respiratory[a]	ST	Children, adults, and older adults (0-99 years)
			LT	Adults and older adults (30-99 years)
Respiratory Effects	Hospital Admissions	Respiratory Outcomes	ST	Older adults (65-99 years)
	Emergency Department Visits	Respiratory Outcomes	ST	Children, adults, and older adults (0-99 years)
	Incidence	Asthma Onset[a]	LT	Children (0-17 years)
		Asthma Symptoms	ST	Children (5-17 years)
		Allergic Rhinitis[a]	LT	Children (3-17 years)
		Minor Restricted Activity Days	ST	Adults and older adults (18-64 years)
		School Loss Days	ST	Children (5-12 years)
			ST	Children (9-10 years)

[a]New or updated health endpoint.

2.3.2 Risk Estimates

This section presents the risk estimates identified for the main $PM_{2.5}$ (section 2.3.2.1) and O_3 (section 2.3.2.2) benefits assessments. These lists reflect the application of the available epidemiologic literature (section 2.2) to the identification criteria (section 2.1).

2.3.2.1 $PM_{2.5}$

Table 10. Set of Risk Estimates for Main $PM_{2.5}$ Benefits Assessments

Endpoint	Study Information	Ages	Exposure Duration	Beta Coefficient (SE)[1]
Mortality	Di et al., 2017b	Older adults (65-99 years)	LT	β = 0.0070 (0.0001)
	Turner et al., 2016	Adults (30-99 years)	LT	β = 0.0058 (0.00096)
	Woodruff et al., 2008	Infants (1-12 months)	LT	β = 0.0056 (0.00454)
Hospital Admissions, Cardiovascular	Bell et al., 2015 —ICD 410, omitting 410.x2; 410-414; 426-427; 428; 429; 430-438; and 440-448	Older adults (65-99 years)	ST	β = 0.00065 (0.00009)
Emergency Department Visits, Cardiovascular	Ostro et al., 2016— ICD 390-459	Children older adults (0-99 years)	ST	β = 0.00061 (0.00042)

Endpoint	Study Information	Ages	Exposure Duration	Beta Coefficient (SE)[1]
Acute Myocardial Infarction	Peters et al., 2001	Adults and older adults (18-99 years)	ST	β = 0.02412 (0.00928)
	Pope III et al., 2006 Sullivan et al., 2005 Zanobetti et al., 2009 Zanobetti and Schwartz, 2006	Adults and older adults (18-99 years)	ST	β = 0.00481 (0.00199) β = 0.00198 (0.00224) β = 0.00225 (0.00059) β = 0.0053 (0.00221)
Cardiac Arrest	Ensor et al., 2013 Rosenthal et al., 2008 Silverman et al., 2010	Adults and older adults (0-99 years)	ST	β = 0.00638 (0.00282) β = 0.00198 (0.00502) β = 0.00392 (0.00222)
Stroke	Kloog et al., 2012—ICD 430-436	Older adults (65-99 years)	LT	β = 0.00343 (0.00127)
Hospital Admissions, Respiratory	Bell et al., 2015—ICD 490-492, 464-466, 480-487, 493	Older adults (65-99 years)	ST	β = 0.00025 (0.00012)
	Ostro et al., 2009—ICD 460-519	Children (0-18 years)	ST	β = 0.00275 (0.00077)
Emergency Department Visits, Respiratory	Krall et al., 2013—ICD 480-486, 491, 492, 496, 460-465, 466, 477, 493, 786.07	Children, adults, and older adults (0-99 years)	ST	β = 0.00055 (0.00027) (GA) β = 0.00097 (0.00035) (AL) β = 0.00083 (0.00033) (MO) β = 0.00135 (0.00059) (TX)
Asthma Onset	Tetreault et al., 2016	Children (0-17 years)	LT	β = 0.04367 (0.00088)
Allergic Rhinitis	Parker et al., 2009	Children (3-17)	LT	β = 0.02546 (0.00962)
Lung Cancer	Gharibvand et al., 2017	Adults and older adults (>29 years)	LT	β = 0.03784 (0.01312)
Alzheimer's Disease	Kioumourtzoglou et al., 2016—ICD 331.0	Older adults (>64 years)	LT	β = 0.13976 (0.01775)
Parkinson's Disease	Kioumourtzoglou et al., 2016—ICD 332	Older adults (>64 years)	LT	β = 0.07696 (0.01891)
Asthma Symptoms	Rabinovitch et al., 2006	Children (6-17 years)	ST	β = 0.00200 (0.00148)
Minor Restricted Activity Days	Ostro and Rothschild, 1989	Adults and older adults (18-64 years)	N/A	β = 0.00741 (0.0007)
Work Loss Days	Ostro, 1987	Adults and older adults (18-64 years)	N/A	β = 0.0046 (0.00036)

ST- short-term; LT- long-term, β- beta risk estimate; ICD- International Statistical Classification of Diseases

Notes: Horizontal lines separating studies within an endpoint indicates that the studies are not intended to be pooled.

[1] Risk estimates have been mathematically converted to beta coefficients, which include the increment of pollutant change and allow for more direct comparisons of risk estimates within health endpoints.

2.3.2.2 O_3

Table 11. Set of Risk Estimates for Main O_3 Benefits Assessments

Endpoint	Study Information	Ages	Exposure (Duration; Season; Metric)	Beta Coefficient (SE)[1]
Respiratory Mortality	Zanobetti and Schwartz, 2008	Children, adults, and older adults (0-99 years)	ST; June-August; DA8	β = 0.00083 (0.00023) (warm season)
	Katsouyanni et al., 2009	Children, adults, and older adults (0-99 years)	ST; April-September; MDA1	β = 0.00073 (0.00057) (warm season)
	Turner et al., 2016—ICD 460-519	Adults and older adults (30-99 years)	LT; April-September; MDA8	β = 0.007696 (0.00118) (warm season)
Hospital Admissions, Respiratory	Katsouyanni et al., 2009—ICD 460–519	Older adults (65-99 years)	ST; April-September; MDA1	β = 0.00028 (0.00018) (warm season)
Emergency Department Visits, Respiratory	Barry et al., 2019—ICD 493, 786.07, 460-466, 477, 491, 492, 496, 480–486, 466.1, 466.11, 466.19	Children, adults, and older adults (0-99 years)	ST; January-December; MDA8	β = 0.00118 (0.00040) (Atlanta, GA) β = 0.00118 (0.00059) (Birmingham, AL) β = 0.00195 (0.00049) (Dallas, TX) β = 0.00118 (0.00040) (Pittsburgh, PA) β = 0.00079 (0.00030) (St. Louis, MO-IL)
Asthma Onset	Tetreault et al., 2016	Children (0-17 years)	LT; June-August; MDA8	β = 0.02075 (0.00146) (warm season)
Asthma Symptoms	Lewis et al., 2013	Children (5-17 years)	ST; January-December; MDA8	β = 0.00708 (0.00372) (Cough) β = 0.00764 (0.00410) (Wheeze) β = 0.01140 (0.00505) (Chest tightness) β = 0.00423 (0.00386) (Shortness of breath)
Allergic Rhinitis	Parker et al., 2009	Children (3-17 years)	LT; May-September; DA24	β = 0.01655 (0.00390) (warm season)
Minor Restricted Activity Days	Ostro and Rothschild, 1989 (MRADs)	Adults and older adults (18-64 years)	ST; April-September; MDA1	β = 0.0022 (0.000658)
School Loss Days	Gilliland et al., 2001	Children (5-17 years)	ST; January-June; DA8	β = 0.0078 (0.0044)

ST- short-term; LT- long-term, β- risk estimate (beta); ICD- International Statistical Classification of Diseases; DA8- daily 8-hour average; MDA8- maximum daily 8-hour average; MDA1- maximum daily 1-hour average; DA24- daily 24-hour average
Notes: Horizontal lines separating studies within an endpoint indicates that the studies are not intended to be pooled
[1] Risk estimates have been mathematically converted to beta coefficients, which include the increment of pollutant change and allow for more direct comparisons risk estimates within health endpoints.

3 BASELINE INCIDENCE AND PREVALENCE ESTIMATES

A baseline incidence rate is an estimate of the number of new cases in the assessment location over a specific timespan, typically one year. For example, in 2018 the mortality rate was 868 deaths per 100,000 people in the U.S.[54] The baseline incidence of the health effect is necessary to convert the relative risk of a health effect provided by epidemiologic studies into an estimated number of cases. To derive the total baseline incidence per year, this rate must be multiplied by the corresponding population. Continuing with the above example, there were 327 million people in the U.S. in 2018, leading to a total baseline incidence of 2.8 million deaths in that year.

Prevalence rates are the proportion of the population experiencing a health endpoint at a point in time. This rate is important when estimating impacts of chronic illnesses, such as asthma, in order to exclude those already diagnosed from the population at risk. For example, if the prevalence of asthmatic children is 8%, only the remaining 92% are at risk of developing asthma.

EPA develops either daily or annual baseline incidence and prevalence rates at the most geographically- and age-specific levels feasible for each health endpoint assessed. For many locations within the U.S., these data are available resolved at the county- or state-level, providing a better characterization of the geographic distribution of hospital and emergency department visits than the national rates. For this update, we focused on developing baseline incidence rates for new health endpoints. Detailed information on baseline incidence data developed previously can be found in Appendix D of the BenMAP-CE User Manual (U.S. EPA, 2018). Importantly, when applying either the daily or annual baseline incidence rates to a health impact estimate, the temporal scale over which the health endpoint was assessed within each study is taken into account. For example, if a long-term O_3 exposure study associated annual deaths with warm-season exposures, full-year baseline incidence rates will be used when estimating benefits.[55]

Table 12 summarizes the sources of baseline incidence rates and provides national average (where used) incidence rates for the endpoints included in the analysis. For both baseline incidence and prevalence data, we used age-stratified rates where available. We applied risk estimates to individual age groups and then sum them over the relevant age range to estimate total population benefits. In some cases we used a single national incidence rate, due to a lack of more spatially disaggregated data, time, or resources. In these cases, whenever possible we used national average rates, because these data are most applicable to a national assessment of benefits. For some studies, however, the only available incidence information comes from the studies themselves; in these cases, incidence in the study population is assumed to represent typical incidence at the national level.

[54] CDC WONDER mortality data; https://www.cdc.gov/nchs/fastats/deaths.htm.

[55] Turner et al., 2016 and Tetreault et al., 2016 risk estimates of long-term O_3-attributable health impacts use full-year baseline incidence rates, even though the exposure period is restricted to the warm season. As such, our baseline incidence rate estimates also reflect the full year for those health endpoints.

Table 12. Baseline Incidence Rates for Use in Impact Functions

Endpoint	Parameter	Rates	
		Value	Source
Mortality[1]	Daily or annual projected incidence to 2060 in 5-year increments (0--99)	Age-, cause-, race-, and county-stratified rates	CDC WONDER (2012–2014) U.S. Census Bureau, 2012
Hospitalizations[2]	Daily incidence rates for all ages	Age-, region/state/county-, and cause- stratified rates	2011-2014 HCUP data files and data requested from and supplied by individual states
Emergency Department Visits[2]	Daily emergency department visit incidence rates for all ages	Age-, region-, state-, county-, and cause-stratified rates	2011-2014 HCUP data files and data requested from and supplied by individual states
Nonfatal Acute Myocardial Infarction	Daily nonfatal AMI incidence rate per person aged 18-99	Age-, region-, state-, and county- stratified rates	AHRQ, 2016
Asthma Symptoms	Daily incidence among asthmatic children Wheeze (ages 5-12) Cough (ages 5-12) Shortness of breath (ages 5-12) Albuterol use (ages 6-13)	 Age- and race- stratified rates 2.2 puffs per day	 Ostro et al., 2001 Rabinovitch et al., 2006
Asthma Onset	Annual incidence 0 - 4 5 - 11 12 - 17	 0.0234 0.0111 0.0044	Winer et al., 2012
Alzheimer's Disease	Daily incidence rates for all ages	Age-, region-, state-, and county- stratified rates	2011-2014 HCUP data files
Parkinson's Disease	Annual incidence 18 - 44 45 - 64 65 - 84 85 - 99	 0.0000011 0.0000366 0.0002001 0.0002483	HCUPnet
Allergic Rhinitis	Respondents aged 3-17 experiencing allergic rhinitis/hay fever symptoms within the year prior to the survey	0.192	Parker et al., 2009

Endpoint	Parameter	Rates	
		Value	Source
Cardiac Arrest	Daily nonfatal incidence rates 0 - 17 18 - 39 40 - 64 65 - 99	 0.00000002 0.00000009 0.00000056 0.00000133	Ensor et al., 2013, Rosenthal et al., 2008, Silverman et al., 2010
Lung Cancer	Annual nonfatal incidence 25 - 34 35 - 44 45 - 54 55 - 64 65 - 74 75 - 84 95 - 99	 0.000001746 0.000014919 0.000067463 0.000208053 0.000052370 0.000576950 0.000557130	NCI, 2015 and Gharibvand et al., 2017
Stroke	Annual nonfatal incidence in ages 65-99	0.00446	Kloog et al., 2012
Work Loss Days	Daily incidence rate per person (18–64) Aged 18–24 Aged 25–44 Aged 45–64	 0.00540 0.00678 0.00492	Adams et al., 1999, Table 41; U.S. Census Bureau (2000)
School Loss Days	Rate per person per year, assuming 180 school days per year	9.9	Adams et al., 1999, Table 47
Minor Restricted-Activity Days	Daily MRAD incidence rate per person (18-64)	0.02137	Ostro and Rothschild, 1989, p. 243

CDC-Centers for Disease Control; NHS-National Health Interview Survey

[1]Mortality rates are only available in 5-year increments. The Healthcare Cost and Utilization Program (HCUP) database contains individual level, state and regional-level hospital and emergency department discharges for a variety of International Classification of Diseases (ICD) codes (AHRQ, 2016).

[2]Baseline incidence rates now include corrections from the states of Indiana and Montana.

3.1 MORTALITY

Baseline incidence rate estimates for mortality remain the same as they were for previous benefits assessments (U.S. EPA, 2018). However, information is provided below for reference. Notably, the Turner et al., 2016 analysis of long-term O_3-attributable health impacts compares warm-season exposures to full-year baseline incidence rates. As such our baseline incidence rate estimates also reflect the full year.

3.1.1 Mortality Data for 2012-2014

We obtained county-level mortality and population data from 2012-2014 for 11 causes for the contiguous United States by downloading the data from the Centers for Disease Control (CDC) WONDER database.[56]

Since the detailed mortality data obtained from CDC do not include population, we combined them with U.S. Census Bureau population estimates exported from BenMAP. We then generated age-, cause-, and county-specific mortality rates using the following formula:

$$R_{i,j,k} = \frac{D_{i,j,k}(2012)+D_{i,j,k}(2013)+D_{i,j,k}(2014)}{P_{i,k}(2012)+P_{i,k}(2013)+P_{i,k}(2014)}$$

where $R_{i,j,k}$ is the mortality rate for age group *i*, cause *j*, and county *k*; *D* is the death count; and *P* is the population. Additional details about the translation of the CDC WONDER data to age-, cause-, and county-specific mortality rates are provided in the BenMAP-CE User's Manual (U.S. EPA, 2018).

[56] http://wonder.cdc.gov

Table 13. National Mortality Rates (per 100 people per year) by Health Endpoint and Age Group, 2012-2014

Mortality Category	ICD-10 Codes	Infant*	1-17	18-24	25-34	35-44	45-54	55-64	65-74	75-84	85+
Mortality, All Cause	All	0.59396	0.01951	0.07804	0.10665	0.17264	0.40542	0.86162	1.79670	4.62837	13.58034
Mortality, Non-Accidental	A00-R99	0.55495	0.00949	0.01874	0.04112	0.10876	0.33084	0.79395	1.73208	4.49595	13.20867
Mortality, Respiratory	J00-J98	0.01297	0.00102	0.00127	0.00253	0.00570	0.02013	0.06560	0.20585	0.57827	1.42362
Mortality, Chronic Lung	J40-J47, J67	0.00053	0.00032	0.00040	0.00074	0.00186	0.01033	0.04045	0.13873	0.36008	0.68593
Mortality, Lung Cancer	C34	0.00002	0.00001	0.00007	0.00033	0.00282	0.02378	0.07992	0.19701	0.32952	0.31820
Mortality, Ischemic Heart Disease	I20-I25	0.00033	0.00004	0.00039	0.00234	0.01242	0.04854	0.12174	0.25698	0.68000	2.27271
Mortality, Cardio-Pulmonary	I00-I78, J10-J18, J40-J47, J67	0.00539	0.00069	0.00099	0.00214	0.00502	0.01794	0.05877	0.18453	0.51055	1.26213
Mortality, NCD + LRI	**	0.18459	0.00618	0.01168	0.02751	0.08129	0.26214	0.63767	1.37694	3.44731	9.47467
Mortality, Lower Respiratory Infection	A48.1, A70, B97.4-B97.6, J09-J15.8, J16, J20-J21, P23.0-P23.4, U04	0.00269	0.00618	0.01168	0.00030	0.00062	0.00112	0.00196	0.00300	0.00758	0.02693
Mortality, Cerebro-vascular	G45-G46.8, I60-I63.9, I65-I66.9, I67.0-I67.3, I67.5-I67.6, I68.1-I68.2, I69.0-I69.3	0.00116	0.00012	0.00034	0.00096	0.00314	0.00809	0.01455	0.02892	0.08553	0.20863
Mortality, COPD	J40-J44, J47	0.00048	0.00005	0.00004	0.00015	0.00102	0.00904	0.03888	0.13689	0.35661	0.67457

*We estimate post-neonatal mortality (deaths after the first month) for infants because the health impact function (see Appendix E) estimates post-neonatal mortality.
**For a full list of codes for non-communicable diseases (NCD) and lower respiratory infections (LRI), see the IHME GBD Code mapping: http://ghdx.healthdata.org/record/ihme-data/gbd-2017-cause-icd-code-mappings.

3.1.2 Mortality Rate Projections 2015-2060

To estimate age- and county-specific mortality rates in years 2015 through 2060, we calculated annual adjustment factors, based on a series of Census Bureau projected national mortality rates (for all- cause mortality), to adjust the age-, county-, and cause-specific mortality rates calculated using 2012-2014 data as described above.[57] We used the following procedure:

For each age group, we obtained the series of projected national mortality rates from 2013 to 2050 (see the 2013 rate in Table 14) based on Census Bureau projected life tables.

We then calculated, separately for each age group, the ratio of Census Bureau national mortality rate in year Y (Y = 2014, 2015, ..., 2060) to the 2013 rate, which is assumed to be representative of the 2012-2014 data and used for the base "year." These ratios are shown for selected years in Table 15.

Finally, to estimate mortality rates in year Y (Y = 2015, 2020, ..., 2060) that are both age-group-specific and county-specific, we multiplied the county- and age-group-specific mortality rates for 2012-2014 by the appropriate ratio calculated in the previous step. For example, to estimate the projected mortality rate in 2015 among ages 18-24 in Wayne County, MI, we multiplied the mortality rate for ages 18-24 in Wayne County in 2012-2014 by the ratio of Census Bureau projected national mortality rate in 2015 for ages 18-24 to Census Bureau national mortality rate in 2013 for ages 18-24.

Table 14. All-Cause Mortality Rate (per 100 people per year), by Source, Year, and Age Group

Source and Year	Infant	1-17	18-24	25-34	35-44	45-54	55-64	65-74	75-84	85+
Calculated CDC 2012-2014	0.594[1]	0.020	0.078	0.107	0.173	0.405	0.862	1.797	4.628	13.580
Census Bureau 2013[2]	0.654	0.029	0.088	0.102	0.183	0.387	0.930	2.292	5.409	13.091

[1]The Census Bureau estimate is for all deaths in the first year of life. EPA benefits assessments uses post-neonatal mortality (deaths after the first month, i.e., 0.23 per 100 people) because the health impact function (see Appendix E) estimates post-neonatal mortality. For comparison purpose, we also calculated the rate for all deaths in the first year, which is 0.684 per 100 people.

[2]For a detailed description of the model, the assumptions, and the data used to create Census Bureau projections, see the working paper, "Methodology and Assumptions for the 2012 National Projections," which is available on http://www.census.gov/population/projections/files/methodology/methodstatement12.pdf

[57] All-cause mortality projections are applied to each cause-specific mortality rate.

Table 15. Ratio of Future Year All-Cause Mortality Rate to 2013 Estimated All-Cause Mortality Rate, by Age Group

Year	Infant	1-17	18-24	25-34	35-44	45-54	55-64	65-74	75-84	85+
2015	0.93	0.93	0.96	1.02	0.96	0.96	1.01	1.02	1.03	1.00
2020	0.94	0.94	0.98	1.04	0.97	0.98	1.02	1.03	1.03	1.00
2025	0.85	0.81	0.74	0.80	0.75	0.77	0.85	0.91	0.93	0.97
2030	0.81	0.75	0.66	0.70	0.67	0.69	0.78	0.86	0.89	0.92
2035	0.76	0.70	0.58	0.62	0.60	0.62	0.71	0.81	0.87	0.87
2040	0.73	0.65	0.51	0.53	0.53	0.56	0.64	0.76	0.84	0.86
2045	0.70	0.60	0.45	0.46	0.46	0.50	0.58	0.71	0.80	0.86
2050	0.67	0.56	0.39	0.40	0.40	0.44	0.53	0.66	0.77	0.87
2055	0.64	0.52	0.34	0.35	0.35	0.39	0.48	0.62	0.73	0.88
2060	0.61	0.48	0.30	0.30	0.31	0.34	0.43	0.58	0.70	0.87

3.1.3 Race-Stratified Incidence Rates

To estimate race-stratified and age-stratified incidence rates at the county level, we downloaded all-cause mortality data from 2007 to 2016 from the CDC WONDER mortality database.[58] Race-stratified incidence rates were calculated for the following age groups: < 1 year, 1- 4 years, 5-14 years, 15-24 years, 25-34 years, 35-44 years, 45-54 years, 55-64 years, 65-74 years, 75-84 years, and 85+ years. We stratified the data into two race categories, White and Non-White, and follow all methods outlined in section D.1.1 of the BenMAP-CE User Manual (U.S. EPA, 2018). To properly impute incidence rates for suppressed and unreliable counties, we downloaded data at the state, regional, and national scales.

3.2 HOSPITALIZATIONS

The approach for estimating hospitalization baseline incidence rates for new health endpoints is based on HCUP data, developed to match the granularity and timeframe of other hospitalization endpoints used in benefits assessments. New hospitalization endpoints are comprised of new sets of ICD-9 codes that correspond to newer studies evaluating air pollution-attributable hospitalizations. Detailed information is provided below and available in the BenMAP-CE User Manual (U.S. EPA, 2018).

Hospitalization rates were calculated using data from the Healthcare Cost and Utilization Project (HCUP). HCUP is a family of health care databases developed through a Federal-State-Industry partnership and sponsored by the Agency for Healthcare Research and Quality (AHRQ). HCUP products include the State Inpatient Databases (SID), the State Emergency Department Databases (SEDD), the Nationwide Inpatient Sample (NIS), and the Nationwide Emergency Department Sample (NEDS).

The level of hospitalization data available differs by state. While many states provide granular discharge-level data, others may only provide county- or state level-data. Also, 14 states, mostly in the southeast,

[58] http://wonder.cdc.gov

do not provide data to HCUP. For these states, regional statistics from HCUPnet[59] were used to estimate baseline hospitalization rates.

HCUP categorizes hospital admissions in various ways. Hospitalization admission types used when reporting data to HCUP include emergency (admitted from the emergency department), urgent (admitted from another hospital), elective (admitted from another health facility, including long-term care), newborn (admitted for delivery), trauma (not used by all states), and other/missing/invalid. As $PM_{2.5}$ and O_3 exposure predominantly leads to cardiovascular and respiratory health effects, we provide some information on the proportion of these types of hospitalizations, based on an analysis of hospitalizations from the state of Florida in 2014. Florida was selected for this analysis as it was the most populated state providing details regarding hospital admission type.

- Emergency hospital admissions comprise approximately 80% of cardiovascular and 85% of respiratory admissions
- Urgent hospital admissions comprise approximately 10% of cardiovascular and 8% of respiratory admissions
- Elective hospital admissions comprise approximately 10% of cardiovascular and 7% of respiratory admissions
- Newborn hospital admissions comprise no cardiovascular and respiratory admissions
- Trauma hospital admissions comprise approximately 0.1% of cardiovascular and respiratory admissions
- Other/missing/invalid hospital admissions comprise no cardiovascular or respiratory admissions

All hospital admission baseline incidence data used in this analysis (and input into BenMAP-CE) reflects total hospital admissions, due to time constraints limiting the ability to separate types (e.g., emergency, urgent, elective, etc) within HCUP data by various states and regions. However, the breakdown of hospital admission types generally reflects the types of health endpoints associated with air pollution exposures, with the majority of effects falling into the emergency and urgent types (e.g., heart or asthma attack) with a small subset potentially leading to elective hospital admissions (e.g., exacerbation of heart failure).

Health endpoints in hospitalization studies are defined using different combinations of ICD codes corresponding to specific diagnoses. Some span large categories of diagnoses, such as all cardiovascular or all respiratory admissions, while others reflect specific conditions, including Alzheimer's disease and Parkinson's disease.[60] For each ICD code combination, unique baseline incidence rates are developed.

[59] HCUPnet is a free, on-line query system based on data from HCUP. It provides access to summary statistics at the state, regional and national levels.

[60] Parkinson's disease incidence rates were developed in a slightly different manner, due to time and resource limitations. We develop regional and age-specific incidence rates for Parkinson's disease hospital admissions using the HCUPnet SID, which provides the total number of hospital visits in the U.S. by age group and region, separately. We first calculate the distribution of annual hospital visits across HCUPnet's 6 age groups: less than 1, 1 to 17, 18 to 44, 45 to 64, 65 to 84, and above 85 years old. Since Parkinson's disease typically affects older adults, hospitalization counts are unavailable for the age groups below 18 years old. We apply the national age distribution to the regional hospitalization totals to estimate the annual number of hospital visits by region and age. We then divide the regional and age-specific counts by the regional and age-specific population and by 365 to

3.3 EMERGENCY DEPARTMENT VISITS

As new studies evaluating air pollution-attributable emergency department utilizing new sets of ICD-9 codes were identified for use in benefits assessment here, we developed corresponding new emergency department baseline incidence rates. Similar to hospitalization baseline incidence rates, the approach for estimating emergency department visit baseline incidence rates also utilizes HCUP data and remains the same as in previous benefits assessments, details for which can be found in the BenMAP-CE User Manual (U.S. EPA, 2018). Information is provided below for reference.

Similar to hospitalization rates, the data source for emergency department/room visits is also HCUP, (i.e., SID, SEDD, and NEDS), states vary by level of data provided (i.e., discharge-, county-, state, and regional-level), and unique baseline incidence rates are generated for each health endpoint ICD code combination.

3.4 HEALTH ENDPOINT ONSET/OCCURRENCE

Baseline incidence estimates for health endpoint onset or occurrences are described below, listed in alphabetical order. Onset indicates the development of a health endpoint (e.g., asthma diagnosis), whereas occurrence refers to an instance of that health endpoint (e.g., asthma attack).

3.4.1 Acute Myocardial Infarctions (AMIs)

Baseline incidence rate estimates for AMIs remain the same as they were for previous benefits assessments. However, detailed information is provided below for reference.

The relationship between short-term particulate matter exposure and heart attacks was originally quantified in a case-crossover analysis by Peters et al., 2001 and supplemented with evidence found in more recent single and multi-city studies (Pope III et al., 2006, Sullivan et al., 2005). The population in the original study was identified from heart attack survivors in a medical clinic. Therefore, the applicable population to apply to the risk estimate is all individuals surviving a heart attack in a given year. Several data sources are available to estimate the number of heart attacks per year. For example, several cohort studies have reported estimates of heart attack incidence rates in the specific populations under study. However, these rates depend on the specific characteristics of the populations under study and may not be the best data to extrapolate nationally. The American Heart Association reports approximately 785,000 new heart attacks per year (Roger et al., 2012). Exclusion of heart attack deaths reported by CDC Wonder yields approximately 575,000 nonfatal cases per year.

An alternative approach to the estimation of heart attack rates is to use data from the Healthcare Cost and Utilization Project (HCUP), assuming that all heart attacks that are not instantly fatal will result in a hospitalization. Details about HCUP data are described in Section D.2 of the BenMAP-CE User Manual (U.S. EPA, 2018). According to the 2014 HCUP data there were approximately 608,795 hospitalizations due to heart attacks (acute myocardial infarction: ICD-9 410, primary diagnosis). We estimated baseline rates based on HCUP data rather than extrapolating from cohort studies because HCUP is a national database with a larger sample size intended to provide reliable national estimates. The incidence rate calculation is also described in Section D.2 of the BenMAP-CE User Manual and the incidence rates for

calculate the daily incidence rates. To generate county level incidence rates, we assume that each county has the same incidence rate as the region it falls within.

AMI hospitalization are presented in Table D-5. An alternative approach to the estimation of AMI rates is to use data from HCUP and assume that all AMIs that are not instantly fatal will result in a hospitalization.

It is important to note that when calculating the incidence of nonfatal AMIs, the fraction of fatal heart attacks is subtracted to ensure that there is no double-counting with mortality estimates. Specifically, we apply an adjustment factor in the risk estimate to reflect the probability of surviving a heart attack. The adjustment factor comes from Rosamond et al., 1999, which reported that approximately 6% of male and 8% of female hospitalized AMI patients die within 28 days (either in or outside of the hospital). Therefore, we applied a factor of 0.93 to the estimated number of PM-related AMIs to exclude the number of cases that result in death within the first month. Note that we did not adjust for fatal AMIs in the incidence rate estimation, due to the way that the epidemiological studies are designed. Those studies consider total admissions for AMIs, which includes individuals living at the time the studies were conducted. We use the definition of AMI that matches the definition in the epidemiological studies. Age-specific baseline incidence rates are based on data from the Agency for Healthcare Research and Quality's HCUP NIS database (AHRQ, 2016). We identified death rates for adults hospitalized with AMI stratified by age (e.g., 1.852% for ages 18-44, 2.8188% for ages 45-64, and 7.4339% for ages 65+). These rates show a clear downward trend over time between 1994 and 2009 for the average adult and thus replace the 93% survival rate previously applied across all age groups from Rosamond et al., 1999.

3.4.2 Asthma Onset and Symptoms

3.4.2.1 Asthma Onset

Baseline incidence rates for new asthma onset are estimated from Winer et al., 2012. Winer et al., 2012 identify newly diagnosed asthma from the 2006-2008 Asthma Call-Back Survey (ACBS) and Behavioral Risk Factor Surveillance System (BRFSS) as individuals diagnosed by a doctor, or other health professional, within the 12 months prior to the surveys. Table 12 details the breakdown, by age, of the annual national incidence rates for asthma onset.

For the set of endpoints affecting the asthmatic population, in addition to baseline incidence rates, prevalence rates of asthma in the population are needed to define the applicable population. We derive asthma prevalence data from the National Health Interview Survey (NHIS).[61] For functions with age ranges that do not align with the ranges reported in the NHIS data table, we develop a weighted-average prevalence rate for the age range, where the weights are the number of years that overlap with each NHIS age group. Table 16 provides the breakdown of the 2018 NHIS rates used to calculate the weighted averages. Table 17 details the resulting weighted averages by study and age group. Note that these reflect recent asthma prevalence and assume no change in prevalence rates in future years.

[61] https://www.cdc.gov/asthma/nhis/2018/data.htm and
https://www.cdc.gov/asthma/most_recent_national_asthma_data.htm

Table 16. Asthma Prevalence Rates

NHIS Age Group	Asthma Prevalence Rate
0 - 4	0.038
5 - 11	0.081
5 - 14	0.086
12 - 17	0.099
15 - 19	0.110
20 - 24	0.081
0 - 17	0.075

Table 17. Weighted Average Asthma Prevalence by Study

Endpoint	Ages	Author[1]	Pollutant	Weighted Prevalence
Asthma Onset	0 – 4	Tetreault et al., 2016	$PM_{2.5}$	0.0380
	5 - 17	Tetreault et al., 2016	$PM_{2.5}$	0.0893
	0 - 17	Tetreault et al., 2016	O_3	0.0750
Asthma symptoms, albuterol use	6 - 13	Rabinovitch et al., 2006	$PM_{2.5}$	0.0860
[1]Prevalence rate derived for albuterol use must be loaded into BenMAP-CE as part of a separate incidence or prevalence dataset, unlike the remainder of the rates, which are embedded within the health impact functions.				

3.4.2.2 Albuterol Use

We develop incidence rates for albuterol use from the rates presented in Rabinovitch et al., 2006, the same study from which the risk estimate was developed. As described in the 'Recommended Set of Health Endpoints and Health Impact Functions' section, Rabinovitch et al., 2006 analyzed the relationship between short-term $PM_{2.5}$ exposure and asthma exacerbation in children ages 6 to 13 years old. The authors use an electronic inhaler to record the number of actuations ('puffs') for each 24-hour period and calculate an average albuterol use rate of 2.2 'puffs' per child per day.

As described in section 3.4.2.1, in addition to the baseline incidence rates, we apply a weighted-average asthma prevalence rate of 0.086, based on the 5-14 age group, using the NHIS prevalence data to identify the applicable population.

3.4.2.3 Asthma Symptoms

We develop incidence rates for asthma symptoms using the estimates presented in Lewis et al., 2013, the same study from which the concentration-response function was developed. As described in the 'Recommended Set of Health Endpoints and Health Impact Functions' section, Lewis et al., 2013 studied the effects of short-term O_3 exposure on frequency of asthma symptoms in an asthmatic population of children ages 5 to 12 years old. The authors estimate the incidence of each asthma symptom using the number of person-days where children reported experiencing the symptom divided by the total number of person-days monitored for that symptom. The percent of days monitored during which children experienced each symptom are calculated as 30.1% for cough, 19.4% for wheeze, 18.5% for shortness of breath, and 12.7% for chest tightness. Therefore, the national incidence rates of asthma symptoms are 0.301 for cough, 0.194 for wheeze, 0.185 for shortness of breath, and 0.127 for chest tightness.

'Prevalence rates for asthma symptoms remains the same as in previous benefits assessments (previously referred to as asthma exacerbation) (Table 16).

3.4.3 Allergic Rhinitis

We develop prevalence rates for hay fever/rhinitis using the estimates presented in Parker et al., 2009, the same study from which the concentration-response function was developed. As described in the 'Recommended set of Health Endpoints and Health Impact Functions' section, Parker et al., 2009 investigates the associations between long-term ozone exposure and respiratory allergies in children ages 3 to 17 years old. The authors use prevalence data from the NHIS household interview survey and define allergic rhinitis as children with reported hay fever, respiratory allergy, or both within the 12 months prior to the survey. Of the eligible population (72,279), 19.2% of respondents experience allergic rhinitis symptoms within the year prior to the survey, therefore, the national prevalence rate of hay allergic rhinitis is 0.192.

3.4.4 Lung Cancer

We use the existent baseline incidence rate for lung cancer mortality in combination with the five-year lung cancer survival rate from NCI, 2015 to develop baseline incidence rates for non-fatal lung cancer. We first use the five-year lung cancer survival rate to calculate the total incidence of lung cancer (both fatal and non-fatal) from the baseline mortality rate using the following formula: baseline mortality rate / (1 – five-year survival rate). We then calculate the incidence of non-fatal lung cancer as the difference between total lung cancer incidence and fatal lung cancer incidence (NCI, 2015). presents the baseline incidence of lung cancer mortality, the SEER five-year survival rate, the estimated total lung cancer incidence, and the estimated non-fatal lung cancer incidence rate by age group.

Table 18. Lung Cancer Incidence Rates

Age Group	Annual Lung Cancer Mortality Incidence [A]	Five-Year Survival Rate [B]	Total Lung Cancer Incidence [C] = [A] / (1 - [B])	Non-fatal Lung Cancer Incidence [D] = [C] – [A]
25-34	0.0000033	34.6%	0.0000050	0.00000175
35-44	0.0000282	34.6%	0.0000431	0.00001492
45-54	0.0002378	22.1%	0.0003053	0.00006746
55-64	0.0007922	20.8%	0.0010003	0.00020805
65-74	0.00019701	21.0%	0.0002494	0.00005237
75-84	0.0032952	14.9%	0.0038722	0.00057695
85+	0.0031820	14.9%	0.0037391	0.00055713

3.4.5 Minor Restricted Activity Days (MRAD)

The incidence estimate for this health endpoint remains the same as in previous benefits assessments. Ostro and Rothschild, 1989 (p. 243) provide an estimate of the annual incidence rate of MRADs per person of 7.8.

3.4.6 School Loss Days

Baseline incidence rate estimates for school loss days remain the same as they were for previous benefits assessments. However, detailed information is provided below for reference.

We have two sources of information to use when estimating the baseline incidence rates of missed school days: the National Center for Education Statistics (NCES), which provided an estimate of all-cause school loss days, and the National Health Interview Survey (NHIS) (Adams et al., 1999, NCES, 1996, Table 47), which has data on different categories of acute school loss days. Table 19 presents the estimated school loss day rates. Further detail is provided below on these rates.

Table 19. School Loss Day Rates (per student per year)

Type	Northeast	Midwest	South	West
Respiratory illness-related absences	1.3	1.7	1.1	2.2
Illness-related absences	2.4	2.6	2.6	3.7
All-cause	9.9	9.9	9.9	9.9

*Illness-related school loss day rates were based on data from the 1996 NHIS and an estimate of 180 school days per year, excluding school loss days due to injuries. All-cause school loss day rates were based on data from the NCES.

3.4.6.1 All-Cause School Loss Day Rate

Based on data from the U.S. Department of Education (1996, Table 42-1), the National Center for Education Statistics estimates that for the 1993-1994 school year, 5.5% of students are absent from school on a given day. This estimate is comparable to study-specific estimates from Chen et al., 2000 and Ransom and Pope, 1992, which ranged from 4.5% to 5.1%.

3.4.6.2 Illness-Related School Loss Day Rate

The National Health Interview Survey (NHIS) has regional estimates of school loss days due to a variety of acute conditions (Adams et al., 1999). NHIS is a nationwide sample-based survey of the health of the noninstitutionalized, civilian population, conducted by NCHS. The survey collects data on acute conditions, prevalence of chronic conditions, episodes of injury, activity limitations, and self-reported health status. However, it does not provide an estimate of all-cause school loss days.

In estimating illness-related school loss days, we started with school loss days due to acute problems (Adams et al., 1999, Table 47) and subtracted lost days due to injuries, in order to match the definition of the study used in the risk estimate to estimate illness-related school absences (Gilliland et al., 2001). We then divided by 180 school days per to estimate illness-related school absence rates per school day. Similarly, when estimating respiratory illness-related school loss days, we use data from Adams et al., 1999, Table 47. Note that we estimated 180 school days in a year to calculate respiratory illness-related school absence rates per year.

3.4.7 Work Loss Days

The incidence estimate for this health endpoint remains the same as in previous benefits assessments. The yearly work-loss-day incidence rate per 100 people is based on estimates from the 1996 National Health Interview Survey (Adams et al., 1999, Table 41). They reported a total annual work loss days of 352 million for individuals ages 18 to 65. The total population of individuals of this age group in 1996 (162 million) was obtained from (U.S. Census Bureau, 1998). The average annual rate of work loss days

per individual is 2.17. Using a similar approach, we calculated work-loss-day rates for ages 18-24, 25-44, and 45-64, respectively.

4 DEMOGRAPHIC INFORMATION

Quantified and monetized human health impacts are calculated using information regarding the demographic characteristics of the population exposed to air pollution; these data include the age, sex, race/ethnicity and location of the population. We use population projections based on economic forecasting models developed by Woods and Poole, Inc. (Woods & Poole, 2015). The Woods and Poole (WP) database contains county-level projections of population by age, sex, and race out to 2050, relative to a baseline using the 2010 Census data. Projections in each county are determined simultaneously with every other county in the U.S to take into account patterns of economic growth and migration.

The sum of growth in county-level populations is constrained to equal a previously determined national population growth, based on Bureau of Census estimates (Hollmann et al., 2000). According to WP, linking county-level growth projections together and constraining to a national-level total growth avoids potential errors introduced by forecasting each county independently. County projections are developed in a four-stage process:

1. National-level variables such as income, employment, and populations are forecasted.
2. Employment projections are made for 179 economic areas defined by the Bureau of Economic Analysis (U.S. BEA, 2004), using an "export-base" approach, which relies on linking industrial-sector production of non-locally consumed production items, such as outputs from mining, agriculture, and manufacturing with the national economy. The export-based approach requires estimation of demand equations or calculation of historical growth rates for output and employment by sector.
3. Population is projected for each economic area based on net migration rates derived from employment opportunities and following a cohort-component method based on fertility and mortality in each area.
4. Employment and population projections are repeated for counties, using the economic region totals as bounds. The age, sex, and race distributions for each region or county are determined by aging the population by single year of age by sex and race for each year through 2050 based on historical rates of mortality, fertility, and migration.

5 HEALTH ENDPOINT VALUATION

To directly compare benefits estimates associated with a rulemaking to cost estimates, the number of instances of each air pollution-attributable health impact must be converted to a monetary value. This requires a valuation estimate for each unique health endpoint, and potentially also discounting if the benefits are expected to accrue over more than a single year, as recommended by the U.S. EPA, 2014.

As reductions in ambient concentrations of air pollution generally lower the risk of future adverse health effects by a small amount for a large population, the most appropriate economic measure is the ex ante (before the effect has occurred) willingness-to-pay (WTP) for changes in risk. WTP values are calculated by dividing the monetary value an individual is willing to pay for a specific risk reduction by that change in risk.[62] Using this approach, the size of the affected population is automatically taken into account by the number of incidences predicted by epidemiological studies applied to the relevant population. There are three primary components of the value to society of an individual's avoidance of a non-fatal illness: 1) medical costs, 2) lost productivity, and 3) impacts on quality of life (i.e., "pain and suffering"). Estimates of individual WTP are conventionally thought to reflect all three of these components and are the preferred welfare valuation measure.[63] However, WTP values are available for a very limited subset of health endpoints, such as mortality.[64]

For health endpoints where WTP estimates are not available, such as hospital admissions, we instead use the cost of treating or mitigating the effect to estimate the economic value. Cost-of-illness (COI) estimates are generally considered to be a lower bound estimate of the true value of reducing the risk of a health effect because they reflect the direct expenditures related to treatment and in some cases costs such as associated productivity losses, but not the value of avoided pain and suffering (Berger et al., 1987, Harrington and Portney, 1987, U.S. EPA, 2014). Additionally, COI estimates require additional parsing of individual health endpoints. For example, a stroke may initially involve an emergency department visit and hospitalization, but will also likely include additional follow-up medical costs, such as doctor visits and medications.

To prevent double counting of health impacts, when estimating monetary valuations, health endpoints are separated into the following non-overlapping categories: mortality (section 5.1), hospital admissions, emergency department visits (section 5.2), and health endpoint onset/occurrence (section 5.3).

EPA develops valuation estimates at the most age-refined level feasible for each health endpoint assessed. While we focused on identifying valuation estimates from peer-reviewed and published literature for new health endpoints, we were also able to update several valuation estimates for endpoints evaluated in previous benefits analyses, such as stroke, cardiac arrest, and AMIs. New hospitalizations and emergency department visits health endpoint valuations reflect specific ICD-9 codes

[62] For example, suppose a measure is able to reduce the risk of mortality from 2 in 10,000 to 1 in 10,000 (a reduction of 1 in 10,000). If individual WTP for this risk reduction is $100, then the WTP for an avoided statistical mortality amounts to $1 million ($100/0.0001 change in risk).

[63] WTP estimates may not fully account for medical costs or lost productivity if individuals assume some related costs would be borne by others (e.g., health insurance providers and employers).

[64] Economic theory also argues that WTP for most goods (such as environmental protection) will increase if real income increases.

evaluated by the epidemiologic study. New onset or follow-up/management health endpoints reflect WTP or COI valuation estimates that exclude death and initial emergency department and hospitalization costs.

These COI measures represent an update to EPA's previous method to producing COI estimates in three important respects (U.S. EPA, 2018):

- Estimates are of the *costs* of medical treatment, rather than *charges* by medical providers.
- Sampling parameters are used in survey data to express statistical uncertainty in mean cost estimates.
- More recent data is being used to reflect current treatment and healthcare costs.

When multiple valuation studies are available, the strengths and limitations of each study are considered, in a manner similar to that described for epidemiologic studies (section 2.1). The criteria for evaluation of these studies are listed in Table 20. In some cases, judgment is required to identify studies for valuation estimates when a similar number of preferred attributes are satisfied by multiple studies.

Table 20. Cost of Illness Economic Study Identification Consideration Factors

Criteria[a]	**Prioritization Detail (In order of most to least preferred)**
Peer-Reviewed Research	Peer-reviewed and published literature only
Endpoint Definition	1. ICD codes align with the epidemiological study 2. ICD codes overlap with the epidemiological study
Population Attributes	Prefer studies that match epidemiological study's population (specifically by age)
Study Period	More recent data are preferred
Measure of Costs[b]	1. Total payments 2. Allowable charges 3. Cost-adjusted charges 4. Unadjusted charges
Study Location	1. Nationwide coverage 2. Multi-city and/or multi-state coverage 3. Local study population
Coverage of cost elements	Studies that account for more cost elements (e.g., treatment settings) and longer time horizons are preferred
Study Size	Larger study size preferred

[a] This table focuses on COI because WTP measures are not currently available for the health endpoints of interest. Had WTP estimates been available, additional criteria would be relevant. It also excludes valuation estimates of hospitalizations and emergency department visits, which are developed by EPA and described in the appendices to U.S. EPA, 2018.
[b]Onukwugha et al., 2016 provides more information on these methods.

We provide unit values for health endpoints (along with information on the distribution of the unit value) in Table 21. All values are in constant year 2015$, adjusted for growth in real income for WTP estimates out to 2024 using projections provided by Standard and Poor's, which is discussed in further detail below. Additional detail regarding the development of each health endpoint valuation is also provided below.

Table 21. Unit Values for Economic Valuation of Health Endpoints (2015$)[1]

Health Endpoint	Type	Central Estimate of Value Per Statistical Incidence (2015$)	Source
Mortality	Value of Statistical Life (VSL)	3%: $7,800,000 7%: $7,100,000	Weibull distribution fitted to 26 published VSL estimates (5 contingent valuation and 21 labor market studies). Underlying studies, distribution parameters, and other information are available in Appendix B of the EPA's *Guidelines for Preparing Economic Analyses* (U.S. EPA, 2014). Adjusted for income growth appropriate to the year of analysis.
Hospitalizations	Medical costs and opportunity cost of time	Varies by ICD codes, ranging between $7,700 and $16,000	HCUP data (details available in section 3.2)
Emergency Department Visits	Medical costs	Varies by ICD codes, ranging between $600 and $1,200	HCUP data (details available in section 3.3)
Nonfatal Myocardial Infarction (AMI)[a]	3-year medical costs[b]	3%: $49,000 7%: $48,000	O'Sullivan et al., 2011
Asthma Symptom- Albuterol Use[c]	Medical costs	$0.35 per albuterol inhaler puff	Average prescription costs derived from Epocrates.com and Goodrx.com accessed March 19, 2020
Asthma Symptom- Chest Tightness, Cough, Shortness of Breath, or Wheeze	WTP for 1 symptom day	$219	Dickie and Messman, 2004
Asthma Onset[c]	Lifetime medical costs and lost productivity	3%: $17,000 7%: $10,000	Belova et al., 2020
Allergic Rhinitis[c]	1-year medical costs	$600	Soni, 2008
Cardiac Arrest[c]	3-year medical costs	3%: $36,000 7%: $35,000	O'Sullivan et al., 2011

Lung Cancer[c]	5-year medical costs	3%: $34,000 7%: $33,000	Kaye et al., 2018
Stroke[c]	1-year medical costs[a]	$34,000	Mu et al., 2017
Work Loss Days	Median daily wage	U.S. median: $150	IEc, 1993
School Loss Days	Lost productivity of parent	$106	US Bureau of Labor Statistics, 2015
Minor Restricted-Activity Days	Median WTP	$70	IEc, 1993

3%- three percent real discount rate; 7%- seven percent real discount rate (OMB, 2003); All estimates rounded to two significant figures.

[a]Valuation estimate has been updated to reflect recent literature.

[b]Excludes initial emergency department and hospitalization costs, which are captured separately.

[c]Valuation estimate is for a new health endpoint.

5.1 MORTALITY

Following the advice of the SAB's Environmental Economics Advisory Committee (SAB-EEAC), the EPA currently uses the value of statistical life (VSL) approach in calculating the core estimate of mortality benefits, because we believe this calculation provides the most reasonable single estimate of an individual's willingness to trade money for reductions in mortality risk (Stavins, 2000). The VSL approach is a summary measure for the value of small changes in mortality risk experienced by a large number of people.

5.1.1 Value of a Statistical Life (VSL)

The current undiscounted VSL used by EPA is $8.7 million (2015$), or $7.8 million (2015$) using a 3% discount rate and $7.1 million (2015$) using a 7% discount rate (U.S. EPA, 2014). This estimate is the mean of a distribution fitted to 26 VSL estimates that appear in the economics literature and that have been identified in the Section 812 Reports to Congress as "applicable to policy analysis" (U.S. EPA, 2011a). It is a value EPA uses in RIAs as well as in the Section 812 Retrospective and Prospective Analyses of the Clean Air Act (U.S. EPA, 2011a).

The VSL approach mirrors that of Viscusi, 1992 and uses the same criteria as in his review of value of statistical life studies. The $8.7 million estimate is consistent with the conclusions of Viscusi, 1992 (updated to 2015$) that "most of the reasonable estimates of the value of life are clustered in the $5.2 to $12.3 million range." Five of the 26 studies are contingent valuation studies, which directly solicit WTP information from subjects; the rest are wage-risk studies, which base WTP estimates on estimates of the additional compensation demanded in the labor market for riskier jobs. Because this VSL-based unit value does not distinguish among people based on the age at their death or the quality of their lives, it can be applied to all deaths. Table 22 presents the central unit value from the 26 value of statistical life studies and their underlying distribution.

Table 22. Central Unit Value for VSL based on 26-value-of-life studies

Basis for Estimate	Age Range at Death		Unit Value (VSL) (2015$)	Distribution of Unit Value	Parameters of Distribution	
	Min	Max			P1	P2
VSL, based on 26 value of statistical life studies	0	99	8,705,114	Weibull	9,648,168	1.509588

5.2 Hospitalizations and Emergency Department Visits

To value hospitalizations, emergency room visits we develop primary COI estimates using data from the Healthcare Cost and Utilization Project (HCUP). The 2016 National Inpatient Sample (NIS) and Nationwide Emergency Department Sample (NEDS) provide recent, nationally representative information on medical treatment in hospitals and emergency departments. In the case of hospital admissions, valuation estimates are calculated as a combination of medical costs and the opportunity cost of time spent at the hospital, measured by lost wages during the hospital stay. In the case of emergency department visits, valuation estimates include only the medical costs. These cost components are summarized in Table 23.

Table 23. Hospitalization and Emergency Department Cost Elements by Endpoint

Endpoint	Medical Costs (Emergency Room)	Medical Costs (Hospital)	Lost Productivity
Hospitalizations		✓	✓
Emergency department visits	✓		
Emergency hospitalizations	✓	✓	✓

The NIS and NEDS datasets include discharge-level observations. That is, each data point represents one individual being discharged from the hospital (NIS) or emergency department (NEDS). Because individuals are treated in these settings for a variety of reasons, we use medical billing codes to extract observations related to each health endpoint. The epidemiological studies described above provide ICD-9 codes for each illness; however, recent HCUP datasets (including NIS and NEDS) use ICD-10 codes. Thus, we first crosswalk the relevant ICD-9 codes to associated ICD-10 codes using a mapping provided by the U.S. Centers for Disease Control.[65] We then identify all discharges in the HCUP datasets with ICD-10 codes that match to a study's ICD-9 code(s).[66] Because HCUP datasets often include multiple ICD-10 codes for each discharge, we focus on the principal diagnosis (i.e., the first-listed ICD-10 code). Other key variables used from HCUP include total charges, cost-to-charge ratio (NIS), and length of stay (NIS).

In the NIS dataset, we convert total charges (i.e., the amount billed to patients, employers, or insurance providers) into estimates of total costs (i.e., the final reimbursements for medical treatment). Unadjusted charges are not suitable for use in regulatory analysis because posted prices generally do

[65] General Equivalence Mapping Files, FY 2016 release of ICD-10-CM. https://www.cdc.gov/nchs/icd/icd10cm.htm.
[66] For emergency hospitalizations, we further restrict the sample to (1) hospitalizations designated as "emergency" and (2) emergency department visits that result in hospitalization.

not reflect actual medical costs due, in part, to negotiation between medical providers and payers (e.g., insurance companies). We assume that adjusted charges reflect the actual revenue the hospital receives and thus the actual cost of providing care. This conversion is completed using hospital-specific cost-to-charge (CCR) ratios provided with NIS. Because CCRs are not available for NEDS, we apply average CCRs for each endpoint in NIS to the same set of ICD-10 codes in NEDS.

For each health endpoint, mean estimates are calculated using estimation commands for survey data to account for the sampling design and sample discharge weights of the HCUP data. This results in estimates of mean costs and a 95% confidence interval, which represents uncertainty in our valuation estimates of medical costs. The resulting estimates are presented in Table 24. Confidence intervals for length of stay cannot be accounted for in the valuation methodology because the EPA's current tool is only capable of reflecting uncertainty in one parameter.

Table 24. Medical Costs and Hospital Stay Data from the HCUP Database

Endpoint	Ages	Epidemiologic Study Author	ICD-9 Codes	Length of Stay in Days (95% CI)[1]	Medical Costs (95% CI) (2015$)[2]
HA, Respiratory-1	0 - 99	Jones et al., 2015	491, 492, 493, 496	3.86 (3.82, 3.90)	$7,676 ($7,574, $7,778)
HA, Respiratory-2	65 - 99	Bell et al., 2015	490-492, 464-466, 480-487, 493	4.66 (4.62, 4.69)	$9,004 ($8,894, $9,113)
HA, All Respiratory	0 - 18	Ostro et al., 2009	460-519	3.50 (3.37, 3.62)	$9,075 ($8,282, $9,868)
HA, All Cardiac Outcomes	0 - 99	Talbott et al., 2014	390-459	5.05 (5.00, 5.11)	$16,045 ($15,721, $16,368)
HA, Alzheimer's Disease	65 - 99	Kioumourtzoglou et al., 2016	331.0	7.95 (7.70, 8.21)	$10,696 ($10,400, $10,992)
HA, Cardio-, Cerebro- and Peripheral Vascular Disease	65 - 99	Bell et al., 2015	426-427,428,430-438, 410-414, 429, 440-448	4.82 (4.78, 4.87)	$14,665 ($14,434, $14,896)
ED, Respiratory	0 - 99	Krall et al., 2013	480-486, 491, 492, 496, 460-465, 466, 477, 493, 786.07	-	$875 ($826, $923)
ED, All Cardiac Outcomes	0 - 99	Ostro et al., 2016	390-459	-	$1,161 ($1,112, $1,210)
ED, Respiratory	0 - 99	Barry et al., 2019	480-486, 491, 492, 496, 460-465, 466, 477, 493, 786.07	-	$875 ($826, $923)

[1]Confidence intervals (CIs) associated with the length of hospital stay are presented for information only and are not used in analyses due to technical limitations. Importantly, the length of stay is a factor in the overall COI estimate.

[2]Medical costs reflect the expenditures per treatment episode/event (e.g., per hospitalization) and confidence intervals (CIs) reflect the 95% CI around the population mean value and not that 95% of patients observe costs within these bounds. Does not include productivity losses.

5.3 HEALTH ENDPOINT ONSET/OCCURRENCE

Monetary valuation estimates for health endpoint onset or occurrences are described below, listed in alphabetical order. Onset indicates the development of a health endpoint (e.g., asthma diagnosis), whereas occurrence refers to an instance of that health endpoint (e.g., asthma attack).

5.3.1 Acute Myocardial Infarctions (AMIs)

Economic values for acute myocardial infarctions (AMIs, also known as heart attacks) have been updated to be derived from O'Sullivan et al., 2011, which estimate three-year medical costs associated with cardiovascular disease events among adults ages 35 and older in the U.S. The authors rely on administrative claims data from a large U.S. health plan and develop econometric models to estimate medical costs for 15 different cardiovascular events, including AMIs. The dataset includes over 20 million commercial and Medical Advantage members between 2002 and 2006. AMIs are identified using the ICD-9 code 410. The authors use propensity score matching to develop a control group with which to compare costs versus individuals that suffered AMIs. We exclude medical costs within the month of the event in an attempt avoid double counting hospitalization costs, which are captured separately in the hospitalization valuation endpoints. Over three years, the total medical costs, excluding hospitalization, are $49,758 (undiscounted, inflated to 2015$), or $48,796 using a 3% discount rate and $47,623 for a 7% discount rate (Table 25). Although this study analyzed costs associated with individuals ages 35 and older, we apply the total medical costs to all ages from zero to 99 since only a small portion (<10%) of annual AMI incidence occurs in the age range below 35.

Table 25. Medical Costs for AMIs (2015$)

Costs	Cumulative Costs	Annual Costs		
		Undiscounted	**3% Discount Rate[1]**	**7% Discount Rate[1]**
*Month of Event**	$43,523	$43,523	$43,523	$43,523
Year 1	$70,629	$27,106	$27,106	$27,106
Year 2	$82,591	$11,962	$11,614	$11,180
Year 3	$93,281	$10,690	$10,076	$9,337
Years 1-3	$93,281	$49,758	**$48,796**	**$47,623**

[1]Uses end-of-year discounting.

We supplement AMI medical costs with estimates of lost earnings using age-specific estimates from Cropper and Krupnick, 1990. Using a 3% discount rate, we estimated the following present discounted values in lost earnings over 5 years due to a heart attack: 0.219 times annual earnings for someone between the ages of 25 and 44, 3.534 times annual earnings for someone between the ages of 45 and 54, and 1.245 times annual earnings for someone between the ages of 55 and 65. The corresponding age-specific estimates of lost earnings using a 7% discount rate are 0.203, 3.287, and 1.158 times annual earnings, respectively. Cropper and Krupnick, 1990 does not provide lost earnings estimates for populations under 25 or over 65. As such we do not include lost earnings in the cost estimates for these age groups. These costs, along with the total valuation estimates for AMIs, are presented in Table 26.

Table 26. Total Valuation Estimates for AMIs (2015$)

Discount Rate	Age Range Min	Age Range Max	Medical Cost	Lost Earnings Multiplier	Total Cost
3%	0	24	$48,796	0	$48,796
	25	44	$48,796	0.219	$48,796 + 0.219*earnings
	45	54	$48,796	3.534	$48,796+ 3.534*earnings
	55	65	$48,796	1.245	$48,796+ 1.245*earnings
	66	99	$48,796	0	$48,796
7%	0	24	$47,623	0	$47,623
	25	44	$47,623	0.203	$47,623+ 0.203*earnings
	45	54	$47,623	3.287	$47,623+ 3.287*earnings
	55	65	$47,623	1.158	$47,623+ 1.158*earnings
	66	99	$47,623	0	$47,623

5.3.2 Allergic Rhinitis (Hay Fever)

Two potential valuation sources for allergic rhinitis were reviewed: Soni, 2008 and Bhattacharyya, 2011. Both studies utilize data from the Medical Expenditure Panel Survey (MEPS) and identify allergic rhinitis (also referred to as hay fever) using ICD-9 code 477. Each study analyzes medical expenditures for differing years, Soni, 2008 for the years 2000 and 2005, and Bhattacharyya, 2011 for the year 2007. Soni, 2008 calculates the cost-of-illness for allergic rhinitis as the mean expenditures for ambulatory care, in-patient services, and prescription medications per person. Bhattacharyya, 2011 calculates the incremental difference in annual healthcare expenditures for individuals with and without allergic rhinitis. Although Bhattacharyya, 2011 uses more recent data, the estimates are not specific to children. Therefore, we derived our COI estimates from the 2005 data presented by Soni, 2008, which are stratified by age group. The resulting COI for allergic rhinitis is $600 for ages zero to seventeen (2015$; Table 21). These COI estimates represent mean annual medical costs for patients with hay fever. Given that the health impact function for this endpoint relates to allergic rhinitis prevalence, these estimates are more applicable than values representing only first-year costs.

5.3.3 Asthma Onset

Belova et al., 2020 estimated the lifetime cost of asthma using data from the 2002 to 2010 Medical Expenditure Panel Survey (MEPS). The authors identify all individuals with current asthma (9,409 out of 158,867 respondents) using the ICD-9 code 493 in the MEPS Medical Conditions Files. Additionally, they identify the date of asthma onset for these individuals. Using the MEPS Medical Events files, which capture most types of medical expenditures (e.g., hospitalizations, emergency room visits, outpatient visits, prescriptions), Belova et al., 2020 estimated annual expenditures by asthma duration and age at onset. The annual healthcare costs for asthma—as measured by healthcare expenditures by all paying parties—vary from $700 to $1,800 for children and $800 to $2,200 for adults (2010$). They extrapolate these values to a lifetime cost stream for an incident chronic asthma case to generate present value estimates by onset age using discount rates of 3% and 7%. Additionally, the authors consider productivity impacts that capture 1) the probability of not being able to work due to health reasons, 2) the impact of asthma on occupational choice, and 3) impact of asthma on weekly earnings.

We adapt the Belova et al., 2020 estimates to align with the age groups 0 to 17, 4 to 21, and 35 to 99.[67] This calculation entails weighting the Belova et al., 2020 age groups by their relative prevalence and propagating the standard errors to derive new uncertainty bounds. The results are summarized in Table 27. Confidence intervals are not provided for productivity losses to mirror the valuation functions in BenMAP-CE, which at present are only capable of reflecting uncertainty in one parameter (in this case, medical costs) (Table 21).

Table 27. Age-adjusted Belova et al., 2020 Estimates of Lifetime Asthma Costs

Age of asthma onset	Discount rate	Healthcare costs (2015$)	Productivity Loss (2015$)
0 – 17	3%	$17,232 ($16,366, $18,097)	$27,426
0 – 17	7%	$10,187 ($9,643, $10,730)	$17,502

5.3.4 Asthma Symptoms/Exacerbation

5.3.4.1 Albuterol Use

As albuterol use is a new measure of $PM_{2.5}$-attributable asthma symptoms, we developed a method for valuing this health endpoint. We estimate the economic value for albuterol use associated with asthma symptoms using prescription prices for albuterol inhalers. Epocrates and GoodRx provide cost and actuation information for four common types of albuterol inhalers in 2020 dollars.[68,69] Both online resources utilize published price lists, purchases, claim records, and pharmaceutical data to provide clinical statistics. Epocrates and the FDA provide cost and actuation information for one additional, less common, albuterol inhaler.[70] We divide the cost of inhalers by the actuations per inhaler to calculate an average cost per actuation across all inhaler types. We then adjust the values to 2015$ using the Consumer Price Index (CPI) for medical care. Since medical cost index data were unavailable for 2020 at the time of these calculations, we used the most recently available index (2019). The resulting value for asthma symptoms, albuterol use is $0.35 per actuation (2015$) (Table 21).

5.3.4.2 Cough, Wheeze, Chest Tightness, and Shortness of Breath

While the risk estimates for both PM2.5- and O3-attributable asthma symptoms were updated, the valuation estimates for cough, wheeze, chest tightness, and shortness of breath are still based on the previous method, using the Dickie and Messman, 2004 analysis of parents' WTP to relieve asthma symptoms in children and adults. The authors derive the WTP estimates from an attribute-based, stated-choice question assessing preferences to avoid acute illness as part of a survey performed in Hattiesburg, Mississippi in 2000. Survey respondents are asked to identify whether they or their child have experienced the following asthma symptoms in the past year: cough with phlegm, shortness of breath with wheezing, chest pain on deep inspiration, and fever with muscle pain and fatigue.

[67] These age groups were selected based on the ages pertaining to the $PM_{2.5}$-related health impact functions. These do not currently align directly with the ozone health impact functions for new onset asthma, but the valuation functions nonetheless cover the age ranges needed to value the ozone health impact functions.
[68] https://online.epocrates.com/drugs searched March 19th, 2020.
[69] https://www.goodrx.com/albuterol searched March 19th, 2020.
[70] https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/205636s006lbl.pdf

Respondents were then assigned one of sixteen illness profiles varying by symptom, symptom duration, in days, as well as discomfort level. Dickie and Messman, 2004 calculate the WTP for children ages zero to seventeen as $219, for one avoided mild symptom-day (2015$). The authors also provide WTP estimates by symptom, however, they represent six avoided symptom-days. Therefore, we apply the same WTP value, for one avoided mild symptom-day, to each asthma symptom endpoint (Table 21).

5.3.5 Cardiac Arrest

The COI for cardiac arrests occurring outside of the hospital is derived from O'Sullivan et al., 2011, who estimate three-year medical costs associated with cardiovascular disease events among adults ages 35 and older in the U.S. The authors rely on administrative claims data from a large U.S. health plan and develop econometric models to predict medical costs for 15 different cardiovascular events, including cardiac arrest, referred to as resuscitated cardiac arrest. The dataset includes over 20 million commercial and Medical Advantage members between 2002 and 2006. Cardiac arrests are identified using the ICD-9 code 427.5. The authors use propensity score matching to develop a control group with which to compare costs versus individuals that suffered cardiac arrest. Medical costs occurring within the month of the event were excluded to avoid double counting hospitalization costs, which are separately captured by the hospitalization valuation functions. Over three years, the total medical costs, excluding hospitalization, are $36,142 (undiscounted, inflated to 2015$), or $35,753 using a 3% discount rate and $35,282 for a 7% discount rate (Table 28 and Table 21).

Table 28. Valuation Estimate for Cardiac Arrests (2015$)

Costs	Cumulative Costs	Annual Costs		
		Undiscounted	**3% Discount Rate**	**7% Discount Rate**
*Month of Event**	*$43,904*	*$43,904*	*$43,904*	*$43,904*
Year 1	$71,901	$27,997	$27,997	$27,997
Year 2	$74,701	$2,800	$2,718	$2,617
Year 3	$80,046	$5,345	$5,038	$4,668
Years 1-3	$80,046	$36,142	**$35,753**	**$35,282**

5.3.6 Lung Cancer

The unit value for non-fatal lung cancer incidence is derived from the direct medical costs of lung cancer treatment estimated by Kaye et al., 2018. This COI value incorporates only direct medical costs and not lost earnings associated with lung cancer incidence because the average age of lung cancer diagnosis is approximately 70 and it is assumed that those aged 65 and older are retired and thus have exited the labor market. Lung cancer treatment costs depend to a large extent on the phase of care, with costs in the initial year of treatment (e.g., $17,422 for males) far exceeding the continuing costs of treatment in subsequent years (e.g., $3,269 for males). We calculate costs over a five-year span, beginning with the initial onset which is occurs with a delay after exposure. The specific lag periods between exposure and onset are discussed in Section 6.4.2. The initial year's treatment cost is summed with four years of continuing annual costs discounted by 3% and 7%.

Furthermore, Kaye et al., 2018 provides separate treatment cost estimates for men and women. The distribution of new lung cancer cases by sex in the United States from Siegel et al., 2019 is

approximately 51% male and 49% female. This distribution of new lung cancer cases was used to weight the sex-specific cost estimates from Kaye et al., 2018 to obtain a combined five-year cost estimate for both sexes. In order to adjust the cost estimate to 2015$ using a medical cost index, we assume that costs presented by Kaye et al., 2018 are in 2010$ as an approximate midpoint of the data years 2007-2012. Altogether, the cost of non-fatal lung cancer incidence over a five-year period is estimated to be $33,809 using a 3% discount rate or $32,548 using a 7% discount rate (Table 21).

For an outcome such as lung cancer, there is an expected time lag between changes in pollutant exposure in a given year and the total realization of health effect benefits, commonly referred to in regulatory analyses as the "cessation lag." The time between exposure and diagnosis can be quite long, on the order of years to decades, to realize the full benefits of the air quality improvements. This latency period is important in order to properly discount the economic value of these health benefits.

To estimate the latency period, we performed a literature search using the keywords "non-fatal lung cancer," "lung cancer," "$PM_{2.5}$," "latency," and "incidence." Five papers that estimate the risk of lung cancer incidence from $PM_{2.5}$ exposure using a latency period were identified. The latency period length and country of the identified papers are summarized in Table 29. Based on estimates of lung cancer latency from the literature, 10 years was the most common latency period estimate found in the literature (i.e., the mode).

Table 29. Latency Periods Used in Lung Cancer Risk Assessment Papers

Study	Latency Period (years)	Location
Gogna et al., 2019	5	Canada
Bai et al., 2020	4; 10	Canada
Kulhanova et al., 2018	10	France
Coleman et al., 2020	10; 15	US
Harrison et al., 2004	20	US

To account for the latency period between air pollution reductions and avoided lung cancer diagnoses in our economic valuation estimates, we developed an age-at-diagnosis cessation lag distribution method based on an approach previously used to estimate avoided cases of kidney cancer in analyses of water quality rules (U.S. EPA, 2017). The method uses lung and bronchus cancer diagnosis age-distribution from the Surveillance, Epidemiology, and End Results Program (SEER). For this model, we assumed that the case reduction distribution would follow the age-pattern of cancer diagnosis between the age at which the exposure change occurs and 99 years. Table 30 shows an example case reduction distribution calculation for an exposure change experienced at 55. SEER estimates 92.2% of lung and bronchus cancer cases occur in individuals 55 years and older. Dividing the percentages in the remaining age bins by 92.2% (the percent of lung and bronchus cancer diagnoses between the age of exposure change and end of lifetime), we find that there is a 24% chance that the risk reductions for a 55-year-old occur between ages 55 and 64, a 37% chance that the case reductions occurs between ages 65 and 74, etc. For distributing avoided cases within an age bin, we assume an equal incidence distribution across years within each bin.

Table 30. Percent Lung and Bronchus Cancer Incidence by Age and Distribution of Risk Reduction by Age for an Exposure Change at 55

Age Group	Percent New Cases per Year by Age*	Percent of New Cases Occurring at or After Age 55[1]
0-20	0	NA
20-34	0.2	NA
35-44	0.9	NA
45-54	6.6	NA
55-64	21.8	24
65-74	34.1	37
75-84	26.6	29
85-99	9.7	11
55-99	92.2	100

*May not sum to 100% due to rounding

[1]Calulcated as the percentage in column 2 divided by 92.2%, where 92.2% is the percentage of lung and bronchus incidence between age 55 and 99.

This and other potential cessation lag distribution models for lung cancer onset are described and compared in section 6.4.2.

5.3.7 Minor Restricted Activity Days (MRADs)

Due to their definition, for the purposes of benefits estimation minor respiratory-restricted activity days (MRRAD) are assumed to constitute all MRADs (Ostro and Rothschild, 1989). While no peer-reviewed studies estimating WTP to avoid a MRRAD are available, a central estimate and upper and lower bounds of WTP to avoid a MRRAD were developed by IEc (IEc, 1993).[71] When estimating benefits associated with an MRAD, we use a triangular distribution centered at the estimate.

Any estimate of mean WTP to avoid a MRRAD (or any other type of restricted activity day other than Work Loss Day (WLD)) will be somewhat arbitrary because the endpoint itself is not precisely defined. Many different combinations of symptoms could presumably result in some minor or less minor restriction in activity. Krupnick and Cropper, 1992 argued that mild symptoms will not be sufficient to result in a MRRAD, so that WTP to avoid a MRRAD should exceed WTP to avoid any single mild symptom. A single severe symptom or a combination of symptoms could, however, be sufficient to restrict activity. Therefore, WTP to avoid a MRRAD should, these authors argue, not necessarily exceed WTP to avoid a single severe symptom or a combination of symptoms. The "severity" of a symptom, however, is similarly not precisely defined; moreover, one level of severity of a symptom could induce restriction of activity for one individual while not doing so for another. The same is true for any combination of symptoms.

Given that there is inherently a substantial degree of arbitrariness in any point estimate of WTP to avoid a MRRAD (or other kinds of restricted activity days), the reasonable bounds on such an estimate must be

[71] IEc, 1993 derived this estimate of WTP to avoid a MRRAD using WTP estimates from Tolley et al., 1986 for avoiding a three-symptom combination of coughing, throat congestion, and sinusitis. This estimate of WTP to avoid a MRRAD, so defined, is $69.58 in 2015$.

considered. By definition, a MRRAD does not result in loss of work. WTP to avoid a MRRAD should therefore be less than WTP to avoid a WLD. At the other extreme, WTP to avoid a MRRAD should exceed WTP to avoid a single mild symptom. The highest IEc midrange estimate of WTP to avoid a single symptom is $28.51 (2015$), for eye irritation. The point estimate of WTP to avoid a WLD in the benefit analysis is $110.62 (2015$). If all the single symptoms evaluated by the studies are not severe, then the estimate of WTP to avoid a MRRAD should be somewhere between $28.51 and $110.62. Because the IEc estimate of $69.58 (2015$) falls within this range (and acknowledging the degree of arbitrariness associated with any estimate within this range), we use the IEc estimate of $69.58 (2015$) (Table 21).

5.3.8 School Loss Days

There is currently one unit value available in BenMAP for school loss days, based on (1) the probability that, if a school child stays home from school, a parent will have to stay home from work to care for the child, and (2) the value of the parent's lost productivity. We first estimated the proportion of families with school-age children in which both parents work, and then valued a school loss day as the probability of a work loss day resulting from a school loss day (i.e., the proportion of households with school-age children in which both parents work) times a measure of lost wages.

From the U.S. Bureau of Labor Statistics (2015) we obtained the rate of participation in the workforce of women with children under 18 years of age. We multiplied this rate (69.9%) by the estimated daily lost wage (if a mother must stay at home with a sick child), based on the median full-time weekly wage among women 25 and older in 2015.[72] This median weekly wage is $759 (2015$).[73] Dividing by five work days per week gives an estimated median daily wage of $152. The expected loss in wages due to a day of school absence in which the mother would have to stay home with her child is estimated as the probability that the mother is in the workforce times the daily wage she would lose if she missed a day = 69.9% of $152, or $106. We currently have insufficient information to characterize the uncertainty surrounding this estimate.

A unit value based on the approach described above is likely to understate the value of a school loss day in four ways. First, it omits WTP to avoid the symptoms/illness which resulted in the school absence. Second, it effectively gives zero value to school absences which do not result in a work loss day. Third, the approach may use a wage rate that is too low by assuming that men do not stay at home with sick children. Fourth, does not account for deleterious effects on student learning and subsequent utility or productivity. The unit value of $106 is therefore considered an "interim" value until such time as alternative means of estimating this unit value become available (Table 22).

5.3.9 Stroke

Mu et al., 2017 estimates COI of non-fatal stroke incidence using direct medical costs incurred during initial hospitalization and the 360 days following hospital discharge. The study identifies individuals experiencing a first-time stroke using ICD-9 codes 434 and 436. The authors analyze medical claims from January 2006 to March 2015 utilizing the retrospective IMS LifeLink PharMetrics Plus database for individuals ages 18 to 65, and Medicare Advantage and Medicare Supplemental Claims for individuals above the age of 65. The authors present acute care and long-term care costs stratified by three

[72] Does not include benefits rate for lost work time.

[73] 2015 median wages were the most recently available data at the time of update. However, many valuation estimates account for income growth, approximating 2020 wages.

discharge classifications: dead at discharge, discharged with disability, and discharged without disability. We estimate the average costs for non-fatal cases by weighting the costs for individuals discharged with disability and without disability by their prevalence (23 and 77 percent, respectively). The resulting COI for non-fatal stroke incidence is $33,962 (2015$) (Table 21). This value reflects one-year medical costs following stroke and does not include hospitalization costs, as these costs are separately captured by hospitalization valuation functions. We reviewed several studies that estimate longer-term medical costs (Goodwin et al., 2011, Lee et al., 2007, Luengo-Fernandez et al., 2012, Nicholson et al., 2016) and concluded that roughly three quarters of costs are incurred in first year after stroke occurrence.[74]

5.3.10 Work Loss Days (WLDs)

Work loss days are valued at a day's wage. BenMAP calculates county-specific median daily wages from county-specific annual wages by dividing by (52*5), on the theory that a worker's vacation days are valued at the same daily rate as workdays. This estimate does not include benefits rate for lost work time. The resulting COI for work loss days varies by county, but has a median value of $150 (2015$) (IEc, 1993).(Table 21).

5.4 Developing Income Growth Adjustment Factors for Health Endpoint Onset/Occurrence

Chapter 4 of the BenMAP-CE User Manual provides instructions for formatting and adding income growth data (U.S. EPA, 2018). These values are used to adjust WTP estimates for growth in real income. As discussed in that chapter, evidence and theory suggest that WTP should increase as real income increases. When reviewing the economic literature to develop income growth adjustment factors, it is important to have an economist assist. For an overview of valuation, see Chapter 7 of the BenMAP-CE User Manual, "Aggregating, Pooling, and Valuing".

Adjusting WTP to reflect growth in real income requires three steps:

1. *Identify relevant income elasticity estimates from the peer-reviewed literature.*
2. *Calculate changes in future income.*
3. *Calculate adjustments to WTP based on changes in future income and income elasticity estimates.*

1. Identifying income elasticity estimates

Income elasticity estimates relate changes in demand for goods to changes in income. Positive income elasticity suggests that as income rises, demand for the good also rises. Negative income elasticity suggests that as income rises, demand for the good falls. We do not adjust COI estimates according to changes in income elasticity due to the fact that COI estimates the direct cost of a health outcome; instead we adjust this metric using inflation factors described above. We include income elasticity estimates specific to the type of health endpoint associated with the WTP estimate for three types of health effects: minor, severe and mortality. Minor health effects are those of short duration. Severe, or chronic, health effects are of longer duration. Consistent with economic theory, the peer reviewed

[74] We did not include the additional 25% of medical costs incurred after the first year post-stroke due to the lack of information on the timing of those additional costs. Without information on when they would be incurred we cannot appropriately discount the estimated medical costs.

literature indicates that income elasticity varies according to the severity of the health effect. A review of the literature revealed a range of income elasticity estimates that varied across the studies and according to the severity of health effect. Table 31 summarizes the income elasticity estimates for minor health effect, severe health effect and mortality. Here we have provided a lower, upper, and central elasticity estimate for each type of health endpoint.

Table 31. Income Elasticity Estimates for Minor Health Effects, Severe Health Effects, and Mortality

Health Endpoint	**Lower Bound**	**Central Estimate**	**Upper Bound**
Minor Health Effect	0.04	0.15	0.30
Severe and Chronic Health Effects	0.25	0.45	0.60
Mortality	0.08	0.40	1.00

2. Calculating changes in future income

The next input to the WTP adjustment is annual changes in future income. The Congressional Budget Office's (2016) ten-year projections of US Gross Domestic Product (GDP) are used to estimate changes in future income. Historical GDP data came from the U.S. Bureau of Commerce's Bureau of Economic Analysis. GDP values were adjusted for inflation as needed using the Implicit Price Deflator annual index, published by the Economic Research Division of the Federal Reserve Bank of St. Louis. We divided the projected change in GDP by the Woods & Poole (2015) projected change in total US population to produce an estimate of the future GDP per capita.

3. Calculating changes in WTP

The income elasticity estimates from Table 31 and the estimated changes in future income may then be used to estimate changes in future WTP for each health endpoint. The adjustment formula follows four steps:

1) $$\varepsilon = \frac{\frac{\Delta WTP}{WTP}}{\frac{\Delta I}{I}} = \frac{(WTP_2 - WTP_1) \times (I_2 + I_1)}{(I_2 - I_1) \times (WTP_2 + WTP_1)}$$

2) $$\varepsilon I_2 WTP_2 + \varepsilon I_2 WTP_1 - \varepsilon I_1 WTP_2 - \varepsilon I_1 WTP_1 = I_2 WTP_2 + I_1 WTP_2 - I_2 WTP_1 - I_1 WTP_1$$

3) $$WTP_2 \times (\varepsilon I_2 - \varepsilon I_1 - I_2 - I_1) = WTP_1 \times (\varepsilon I_1 - \varepsilon I_2 - I_1 - I_2)$$

4) $$WTP_2 = WTP_1 \times \frac{\varepsilon I_1 - \varepsilon I_2 - I_1 - I_2}{\varepsilon I_2 - \varepsilon I_1 - I_2 - I_1}$$

Table 32 summarizes the income-based WTP adjustments used within BenMAP-CE for minor health endpoints, severe health endpoints, and premature mortality. BenMAP-CE applies the “mid” income growth adjustment to the WTP for each corresponding health endpoint. The “low” and “upper” are provided for bounding the “mid” estimate. More information on the uncertainties associated with the choice of income elasticity is provided in section 6.4.3.

Table 32. Income-Based WTP Adjustments by Health Effect and Year

	Minor Health Endpoint			Severe Health Endpoint			Mortality		
Year	Low	Mid	Upper	Low	Mid	Upper	Low	Mid	Upper
1990	1	1	1	1	1	1	1	1	1
1991	0.99943614	0.997887194	0.995778859	0.99648118	0.993674994	0.991575539	0.998872638	0.994375765	0.985998511
1992	1.00027895	1.0010463	1.002093554	1.00174439	1.003141999	1.004191637	1.000557899	1.002792478	1.006995797
1993	1.00083518	1.003135324	1.006280541	1.005231023	1.009435654	1.01260066	1.001670957	1.008382797	1.021089673
1994	1.001928926	1.007252812	1.014558434	1.012117267	1.021917462	1.029330373	1.003861666	1.019458413	1.049366593
1995	1.00252676	1.009508491	1.019107819	1.01589787	1.028799176	1.038584113	1.005059958	1.025558352	1.065144777
1996	1.003553152	1.013389945	1.026960373	1.022416711	1.040715098	1.054657698	1.00711906	1.036109447	1.092786551
1997	1.004830718	1.018236518	1.036808729	1.030580044	1.055725813	1.074997663	1.00968492	1.049381137	1.128201008
1998	1.006105304	1.023088813	1.046717048	1.038779855	1.070903659	1.095668674	1.012248039	1.062778115	1.164700031
1999	1.007476926	1.028329492	1.057473063	1.047665954	1.087466359	1.118347049	1.01500988	1.077371955	1.205345869
2000	1.008633733	1.032765627	1.066622734	1.055212379	1.101626635	1.137836933	1.017342448	1.089827657	1.24079144
2001	1.008626103	1.032736301	1.066562176	1.05516243	1.101532698	1.137707233	1.01732707	1.089745045	1.240554214
2002	1.008962274	1.034028053	1.069233894	1.057363987	1.105680108	1.143433094	1.018005252	1.093389511	1.251058578
2003	1.009722471	1.036953092	1.075297475	1.062356591	1.115113139	1.156486392	1.019539833	1.10167253	1.275163889
2004	1.010831594	1.041232586	1.084201217	1.069678664	1.129017591	1.175803781	1.021781206	1.11386621	1.31124568
2005	1.011770725	1.044866562	1.091792464	1.075912952	1.140922546	1.192415953	1.023680925	1.12429142	1.342671752
2006	1.012430668	1.047425628	1.097154975	1.080312252	1.149360299	1.204231024	1.025016785	1.131672144	1.36525023
2007	1.01275146	1.048671246	1.099770427	1.08245647	1.153483868	1.210017681	1.025666475	1.135276675	1.376378059
2008	1.012262344	1.04677248	1.095784903	1.079188704	1.147202373	1.201206207	1.024675965	1.12978518	1.359451532
2009	1.01079917	1.041107416	1.083940148	1.069464207	1.12860918	1.175235033	1.021715641	1.113508224	1.310176253
2010	1.011459589	1.043661356	1.089271665	1.073843718	1.136964202	1.186884999	1.023051262	1.120826483	1.332167268
2011	1.011786222	1.044926405	1.091917515	1.076015592	1.141119123	1.192690849	1.023712158	1.124463439	1.343194842
2012	1.012354255	1.047128916	1.096532583	1.079801798	1.148379683	1.202856183	1.024862051	1.130814672	1.362613082
2013	1.012712717	1.048520923	1.099454761	1.082197666	1.15298593	1.209318399	1.025588155	1.134841442	1.375030875
2014	1.013344169	1.050976157	1.104618788	1.086428881	1.161142945	1.220786929	1.026867747	1.141967177	1.397211194
2015	1.014022827	1.053619623	1.110193372	1.090992332	1.169972539	1.233237505	1.02824378	1.149673343	1.421498775
2016	1.014274955	1.054602981	1.11227107	1.092692018	1.173269868	1.237896562	1.028755188	1.152549148	1.430643797
2017	1.014827728	1.056761265	1.116838455	1.096426606	1.180531025	1.248175263	1.029876947	1.158878565	1.45092845
2018	1.015322924	1.058697701	1.120945096	1.099781871	1.187074065	1.257459402	1.030882478	1.164577603	1.469381213
2019	1.015639186	1.059935808	1.123574972	1.101929545	1.191271544	1.263426423	1.031524897	1.168231487	1.48130703
2020	1.015908599	1.060991406	1.125819683	1.103761792	1.194858909	1.268532872	1.032072306	1.171352863	1.491554141
2021	1.016283393	1.062461257	1.128949761	1.106315613	1.199867845	1.275673389	1.032834172	1.175709248	1.505947828
2022	1.016681671	1.064024925	1.132284641	1.109035254	1.205213666	1.283308029	1.03364408	1.180356026	1.521420956
2023	1.017086029	1.065614223	1.135679722	1.11180234	1.210665345	1.291108131	1.034466624	1.185091853	1.53731966
2024	1.017486334	1.067189336	1.139050007	1.114547729	1.216086745	1.298879623	1.035281181	1.189798594	1.553251266
2025	1.017879009	1.068736196	1.142365217	1.117246628	1.221428633	1.306551456	1.036080599	1.194433689	1.56906867
2026	1.018263578	1.070252538	1.145620227	1.119895339	1.226682782	1.314110994	1.036863804	1.198989868	1.584743023

6 CHARACTERIZING UNCERTAINTY AND EVALUATING SENSITIVITY TO ALTERNATE ASSUMPTIONS

Complex analyses such as the one presented in the final RIA for the Revised CSAPR Update rule use many estimated parameters and inputs. The approach for estimating $PM_{2.5}$ and O_3 benefits includes health effect risk estimates from epidemiologic studies, population data, population growth estimates, economic data for monetizing benefits, and assumptions regarding the future state of the world (i.e., on-the-books regulations). When the uncertainties from each stage of the analysis are compounded, even small uncertainties can have large effects on the total quantified benefits.

After reviewing the EPA's approach to quantifying benefits, the National Research Council (NRC) (2002, 2008) highlighted the need to conduct rigorous quantitative analyses of uncertainty and to present benefits estimates to decision makers in ways that foster an appropriate appreciation of their inherent uncertainty. Since the publication of these reports, the EPA has continued improving its techniques for characterizing uncertainty in the estimated air pollution-attributable benefits.

In light of these recommendations, we incorporate new quantitative and qualitative characterizations of uncertainty. Where possible, we quantitatively assess uncertainty in each input parameter (for example, we characterize statistical uncertainty by performing Monte Carlo simulations). We invest the time and resources in performing the most comprehensive uncertainty analyses for those input parameters that most greatly influence on the size of the estimated health impacts.[75]

In some cases, this type of quantitative analysis is not possible due to lack of data, so we instead characterize the sensitivity of the results to alternative plausible input parameters. And, for some inputs into the benefits analysis, such as the air quality data, we lack the data to perform either a quantitative uncertainty analysis or sensitivity analysis.

Sections 6.1 and 6.2 quantitatively describe the uncertainty associated with estimated $PM_{2.5}$ and O_3-attributable incidence. Section 6.3 provides information on the sensitivity to more granular baseline incidence rates. Section 6.4 quantitatively discusses the influence of uncertainty in the economic valuation functions. Lastly, section 6.5 qualitatively discusses the various potential sources of uncertainty, sometimes including sources of uncertainty touched upon quantitatively.

6.1 QUANTITATIVE CHARACTERIZATION OF $PM_{2.5}$ UNCERTAINTY AND EVALUATING SENSITIVITY TO ALTERNATE $PM_{2.5}$ ASSUMPTIONS

Below we describe our approach for characterizing uncertainty in the estimated $PM_{2.5}$-related effects. We start first with the role of Monte Carlo assessment in generating a quantitative distribution of results. We next describe how alternative risk estimates[76] can be useful for assessing the sensitivity of

[75] Uncertainties that we expect will have the greatest influence on health impacts are 1) those associated with mortality impacts given the severity of the outcome and the associated economic valuation and 2) quantitative and qualitative uncertainty characteristics likely to most strongly impact the magnitude of bias.

[76] Alternate risk estimates are a means to quantitatively understand uncertainties around the main risk estimate. Alternate risk estimates are based on a different set of input parameters, which may come from the same study or different studies. Alternate risk estimates can be used to assess the sensitivity of the risk estimate to alternative assumptions and input parameters, such as modeling choices, populations, or statistical techniques.

the estimated $PM_{2.5}$-related mortality and morbidity to plausible alternative input parameters; this gives insight to the influence of the functional form of the model or alternative epidemiologic approaches. Quantitative sensitivity analyses using alternative or additional risk estimates are included for the following $PM_{2.5}$-attributable health endpoints: mortality in adults (section 6.1.1), asthma onset in children (section 6.1.3), cardiovascular hospital admissions (section 6.1.4), and respiratory hospital admissions (section 6.1.5).

6.1.1 Statistical Uncertainty Around the Risk Estimate (Monte-Carlo Assessment)

For all endpoints analyzed, we use a Monte Carlo simulation in which we sample from the standard error associated with each risk estimate and present the resulting 2.5th and 97.5th percentile values from this distribution as a 95th percentile confidence interval around the estimated health impact and monetized health benefits. Monte Carlo methods are a well-established means of characterizing random sampling error associated with the risk estimates from epidemiological studies. This approach randomly samples from a distribution of incidence and valuation estimates to characterize the effects of uncertainty in those inputs on output variables. The reported standard errors in the epidemiological studies determined the distributions for individual effect estimates for endpoints estimated using a single study. The confidence intervals around the monetized benefits incorporate the epidemiology standard errors as well as the distribution of the valuation function. These confidence intervals do not reflect other sources of uncertainty inherent within the estimates, such as baseline incidence rates, populations exposed, and transferability of the effect estimate to diverse locations. As a result, the reported confidence intervals and range of estimates give an incomplete picture about the overall uncertainty in the benefits estimates.

6.1.2 Adult All-Cause Mortality[77]

Two studies of all-cause, long-term $PM_{2.5}$ exposure and mortality were identified as best characterizing U.S. risk in adults, Di et al., 2017b and Turner et al., 2016. Additional information regarding the cohort concentration exposure distributions (section 6.1.2.1) and additional risk estimates potentially providing insight into the effect of various potential sources of uncertainty, such as different exposure estimation techniques (section 6.1.2.2), confounding by O_3 (section 6.1.2.3), statistical regression techniques and methods to control for confounders (section 6.1.2.4), and effect modification by individual risk factors (section 6.1.6).

6.1.2.1 Low Concentration Exposures

Each epidemiological risk estimate is based on a distribution of air quality concentrations experienced by the original cohort population. As such, it is important to consider the relationship between the concentrations from which the mortality estimates are derived and the concentrations at which the estimates are subsequently applied in future policy scenarios in which concentrations are likely to be lower due to decreasing air pollution trends. When estimating health impacts, we are most confident in results estimated using projected air quality concentrations that closely align with those observed in the epidemiological study from which the risk estimate was obtained (i.e., we are less confident applying risk estimates to pollutant concentrations that do not match the original cohort due to changes in air pollutant concentrations over time). To address the potential mismatch between projected air quality

[77] As estimates of infant mortality incidence are relatively small, we do not perform quantitative uncertainty analyses for that health endpoint.

levels and those in the epidemiologic study, we include air quality information from the original epidemiologic studies where feasible.

Additional information was requested from mortality study authors regarding the ambient concentrations used to estimate exposure of the original cohort.[78] Study authors provided cohort specific $PM_{2.5}$ concentration data at varying levels of detail. $PM_{2.5}$ concentrations for the two long-term exposure epidemiologic cohort studies examining mortality, ACS CSP-II and Medicare are presented in Figure 13 (Di et al., 2017b, Turner et al., 2016). We also included the distribution of $PM_{2.5}$ concentrations from a recent analysis of the CanCHEC cohort in order to compare to some of the lowest reported concentrations in North America (Crouse et al., 2015). Points reflect cohort specific $PM_{2.5}$ concentration data, with connecting lines estimating missing data.

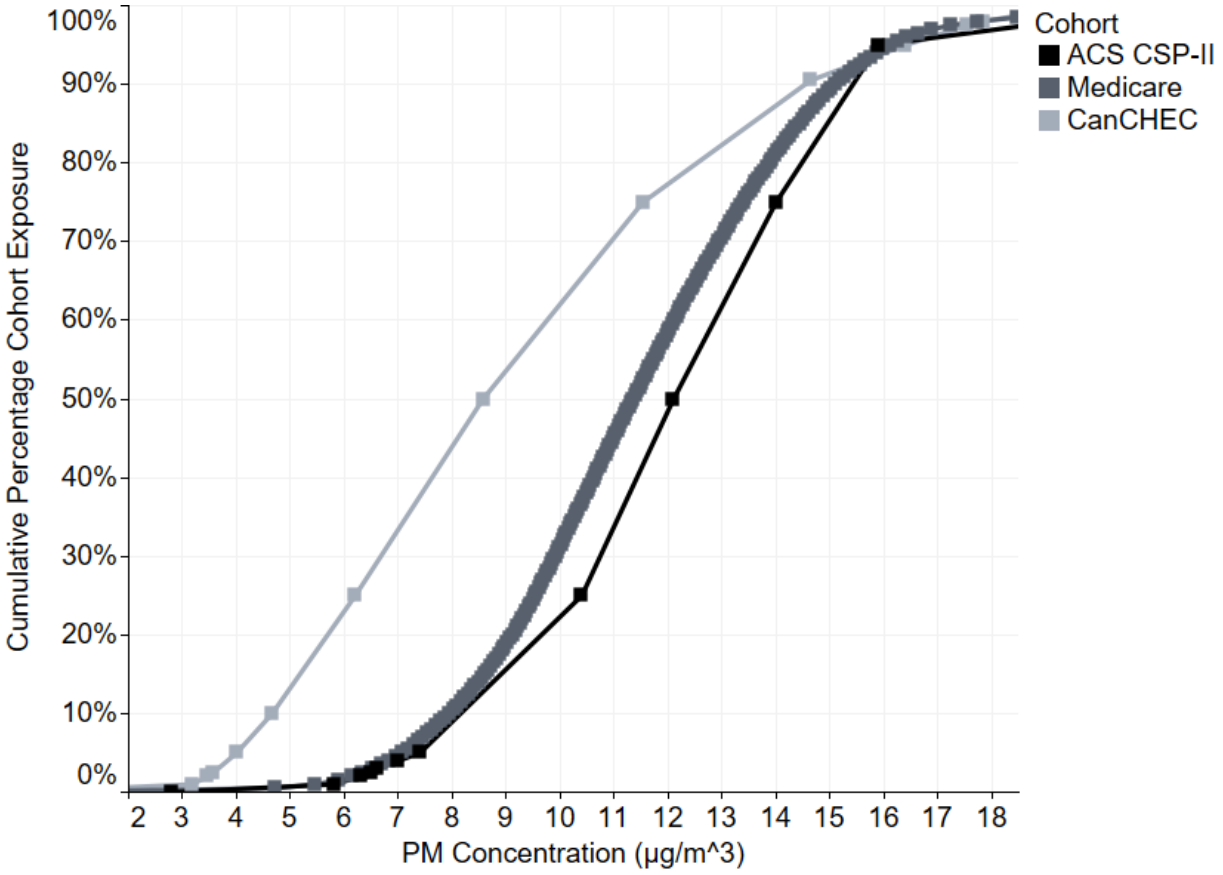


Figure 13. Cumulative Percentile of $PM_{2.5}$ Cohort Exposure from the ACS CSP-II, Medicare, and CanCHEC Cohorts

As air pollution concentrations continue to decline an increasing fraction of the population will be exposed to $PM_{2.5}$ concentrations at the lower end of the air quality distribution experienced by the study cohort. The distribution of $PM_{2.5}$ concentrations for each of three large, long-term exposure cohorts are

[78] For morbidity studies, author-reported air quality information such as the average or mean, standard deviation, and maximum and minimum concentrations were collected and is available in the corresponding Study Information Table.

provided in Table 33. For comparison, the lowest reported $PM_{2.5}$ concentrations from previous studies (Krewski et al., 2009, Lepeule et al., 2012) in which risk estimates were used to estimate all-cause mortality attributed to long-term $PM_{2.5}$ exposure were 5.8 and 8.0 $\mu g/m^3$, whereas the recent studies identified as best characterizing long-term $PM_{2.5}$ exposure and the risk of all-cause mortality include $PM_{2.5}$ concentrations below 3 $\mu g/m^3$ (Di et al., 2017b, Turner et al., 2016).

Table 33. Low Concentration $PM_{2.5}$ Exposures from the ACS CSP-II, Medicare, and CanCHEC Cohorts

Cohort	Percentile of Cohort Exposure ($\mu g/m^3$)										
	0.0%	**1.0%**	**1.5%**	**2.0%**	**2.5%**	**3.0%**	**3.5%**	**4.0%**	**4.5%**	**5.0%**	**10.0%**
ACS CSP-II	2.8	5.8		6.3	6.5	6.6		7.0		7.4	
Medicare	0.0	5.5	5.9	6.1	6.3	6.5	6.7	6.8	6.9	7.1	7.9
CanCHEC	0.0	3.2		3.5	3.6					4.0	4.7

We note that $PM_{2.5}$ concentrations reported in cohort studies are not equivalent to NAAQS design values (DVs). Information relating $PM_{2.5}$ concentrations from cohort studies discussed within this section to $PM_{2.5}$ DVs can be found in section 3.2 of the 2020 PM PA (U.S. EPA, 2020c).

6.1.2.2 Estimating and Assigning Exposures in Epidemiology Studies

New developments in exposure assessment, including hybrid spatiotemporal models that incorporate satellite observations of AOD, land use variables, surface monitoring data from monitors, and chemical transport models, have led to improvements in the spatial resolution and extent of pollutant concentration surfaces. After reviewing the current state of exposure science, the 2019 PM ISA stated that "a number of studies demonstrate that the positive associations observed between long-term $PM_{2.5}$ exposure and mortality are robust to different methods of assigning exposure" and the 2020 O_3 ISA articulated that "hybrid methods have produced lower error predictions of ozone concentration compared with spatiotemporal models using land use and other geospatial data alone but may be subject to overfitting given the many different sources of data incorporated into the hybrid framework."

Although these advancements may reduce bias and uncertainty in risk estimates, the accuracy of hybrid exposure estimates can be difficult to confirm in areas lacking monitors. On the other hand, studies using monitor data as the only exposure information have increasing exposure uncertainty the farther people live from the monitor site.

Di et al., 2017a provided $PM_{2.5}$-attributable mortality risk estimates based on either a hybrid exposure estimation approach combining photochemical air quality modeling with ground-level monitoring data or only on monitoring data. Comparing these two estimates aids in understanding how sensitive long-term, all-cause estimates of $PM_{2.5}$-attributable mortality are to exposure estimation method. A comparison of the risk estimates using either the hybrid or monitor-based exposure estimates is available in Table 34. The italicized risk estimate was identified for use in the main $PM_{2.5}$ benefits assessment.

Table 34. Di et al., 2017a $PM_{2.5}$-Attributable Mortality Risk Estimates per 10 μg/m^3 from Different Exposure Estimation Techniques

Exposure Technique	Risk Estimate
Hybrid Exposure Estimate	*1.073 (1.071, 1.075)*
Monitor-Based Exposure Estimate	1.061 (1.059, 1.063)

Turner et al., 2016 and Pope et al., 2015 analyzed the same ACS CSP-II population over the same time period but used different hybrid exposure estimation techniques. Turner et al., 2016 used the hierarchical Bayesian space–time model (HBM) approach, which combines ambient measurement data with gridded estimates from the CMAQ photochemical model. Pope et al., 2015 used a land use regression model with Bayesian Maximum Entropy kriging of residuals (LURBME). Sensitivity of the risk estimate to the exposure estimation technique is available in Table 35, including the estimate identified for the main benefits assessment in italics.

Table 35. $PM_{2.5}$-Attributable ACS CSP-II Mortality Risk Estimates per 10 μg/m^3 from Different Exposure Estimation Techniques

Exposure Technique	Risk Estimate
HBM	*1.06 (1.04-1.08)*
LURBME	1.07 (1.06–1.09)

6.1.2.3 Confounding by O_3

When considering the relationship between pollutant exposure and health effects, it can be informative to consider whether risk estimates are subjected to confounding when including other pollutants in copollutant models, especially when health impacts of more than two highly correlated pollutants are being estimated concurrently.[79] Regarding long-term exposures, the 2019 PM ISA concluded that "positive associations observed between long-term $PM_{2.5}$ exposure and total mortality remain relatively unchanged after adjustment for O_3, NO_2, and $PM_{10-2.5}$"

Both Turner et al., 2016 and Di et al., 2017a provided single-pollutant and two-pollutant (including O_3 as a copollutant) $PM_{2.5}$-attributable mortality risk estimates. Although the 2019 PM ISA found that, in general, $PM_{2.5}$ risk estimates were relatively unchanged to the inclusion of O_3 in copollutant models, a comparison of risk estimates that either do or do not include O_3 as a copollutant is included to clarify this potential sensitivity with respect to all-cause $PM_{2.5}$-attributable mortality. Differences in the magnitude of risk estimates including or excluding O_3 as a copollutant are provided in Table 36. Italicized risk estimates were identified for use in the main benefits assessment.

Table 36. Single- and Two-Pollutant (Including O_3 as a Copollutant) $PM_{2.5}$-Attributable Mortality Risk Estimates per 10 μg/m^3

	Turner et al., 2016	Di et al., 2017a
Two-Pollutant	*1.06 (1.04-1.08)*	*1.073 (1.071, 1.075)*
Single-Pollutant	1.06 (1.04-1.08)	1.084 (1.081, 1.086)

[79] Modeling more than two correlated pollutants can be problematic due to collinearity issues.

6.1.2.4 Statistical Technique

Di et al., 2017a provided mortality risk estimates using two different statistical methods to adjust for covariates, potentially providing insight into model uncertainties associated with statistical regression techniques. A comparison of the risk estimates using either the generalized estimating equation (GEE) approach, which the authors identified as the main analysis, or the mixed-effects model (COXME) can be found in Table 37.

Table 37. Di et al., 2017a $PM_{2.5}$-Attributable Mortality Risk Estimates per 10 µg/m^3 from Different Statistical Techniques

Statistical Technique	Risk Estimate
GEE	*1.073 (1.071, 1.075)*
COXME	1.081 (1.078, 1.083)

6.1.3 Asthma Onset in Children

For a number of health endpoints we identified plausible alternative risk estimates to characterize the sensitivity of the main risk estimate to alternative assumptions and/or input parameters. Below we detail: 1) the endpoints for which we considered alternative risk estimates; and 2) the studies from which we drew the alternative risk estimates. This type of sensitivity assessment is also performed for other $PM_{2.5}$ and O_3 health endpoints in sections 6.1.4, 6.1.5, and 6.2.4.

The study identified as best characterizing risk for this health endpoint took place in Canada (Tetreault et al., 2016). Even though comparatively Tetreault et al., 2016 was preferred in all identification criteria to other available studies (e.g., study size, exposure estimation technique, study period, etc.) other than location, we thought it useful to include the available U.S.-based risk estimates as uncertainty analyses. An overall comparison of the main risk estimate and 95% confidence interval from Tetreault et al., 2016 and the alternative risk estimates and confidence intervals from McConnell et al., 2010 and Nishimura et al., 2013 can be found in Table 38. Details about the two studies providing alternate risk estimates is below.

Table 38. Potential Sensitivity of Estimated Instances of Asthma Onset

Potential Source of Uncertainty	Potential Insights Gained from Quantitative Uncertainty Analyzes[2]
Application of Risk Estimates to Other Locations and Populations	Tetreault et al., 2016 included only Canadians whereas Nishimura et al., 2013 included five U.S. urban areas and McConnell et al., 2010 was restricted to southern CA
Study Size	Tetreault et al., 2016 included the largest study size, approximately twenty-five times the size of either Nishimura et al., 2013 or McConnell et al., 2010
Study Period	Tetreault et al., 2016 evaluated the most recent health study period (1996-2011) compared to 2002-2006 for McConnell et al., 2010 and 1986-2005 for Nishimura et al., 2013
Exposure Estimate	Tetreault et al., 2016 used hybrid exposure estimates whereas sever states, whereas Nishimura et al., 2013 and McConnell et al., 2010 used monitor-based estimates
Statistical Technique	Tetreault et al., 2016 and McConnell et al., 2010 use time-varying and multilevel Cox proportional hazard models, respectively, whereas Nishimura et al., 2013 uses logistical regression models

Two of the five ISA-identified studies of asthma onset took place in the U.S. (McConnell et al., 2010, Nishimura et al., 2013). McConnell et al., 2010 examined the association between long-term traffic-related air pollution ($PM_{2.5}$, PM_{10}, O_3, and NO_2) exposure and incident asthma in children. The authors collected data for three years from a cohort of 2,497 kindergarten and first-grade children aged 4-9 who entered the Southern California Children's Health Study without asthma or wheeze. McConnell et al., 2010 defined new-onset asthma as physician-diagnosed asthma reported by parents on a yearly questionnaire. While the primary focus of the study was traffic-related air pollution from local vehicle emissions, the authors also utilized ambient air pollution exposure data from central site monitors in each of the 13 communities in the Southern California Children's Health Study. The authors used a multilevel Cox proportional hazards model to estimate the association between ambient air pollution exposure and new-onset asthma, controlling for race/ethnicity, secondhand smoke exposure, and pets in the home. The identified hazard ratio of 1.66 (95% CI: 0.91-3.05) for a 17.4 $\mu g/m^3$ (range of exposure in the 13 communities) increase in annual average $PM_{2.5}$ exposure came from a single pollutant model.

The other study, Nishimura et al., 2013, investigated the relationship between long-term early-life pollution exposure ($PM_{2.5}$, PM_{10}, O_3, NO_2 , and SO_2) and asthma onset in 3,343 Latino and African American children in five urban areas (Chicago, IL; Bronx, NY; Houston, TX; San Francisco, CA; Puerto Rico). The authors obtained data from the Genes–environments and Admixture in Latino Americans (GALA II) Study and the Study of African Americans, Asthma, Genes and Environments (SAGE II). GALA II and SAGE II are case-control studies that enrolled children with and without asthma. The studies defined case subjects as children with physician-diagnosed asthma plus two or more symptoms of coughing, wheezing, or shortness of breath in the two years before study enrollment while control subjects were children with no reported history of asthma, lung disease, or chronic illness, and no reported symptoms of coughing, wheezing, or shortness of breath in the two years before study enrollment. The authors estimated annual average pollution exposures during the first year of life as well as the first three years of life from self-reported residential histories by calculating inverse distance-squared weighted averages

from the four closest U.S. EPA Air Quality System monitoring stations within 50 km. The authors first used regional- and study-specific logistic regression models to estimate the association between asthma diagnosis and pollution exposure, controlling for demographics and socioeconomic status and subsequently combined the regression coefficients into a multi-region estimate using a random-effects meta-analysis. The identified odds ratio of 1.03 (95% CI: 0.90-1.18) for a 1 μg/m^3 increase in average annual $PM_{2.5}$ levels at the residential address during the first year of life came from a single pollutant model. Beta effect coefficients from the main (italicized) and sensitivity analyses are available in Table 39.

Table 39. Beta Coefficients and Standard Errors (SE) from Studies of Examining Long-term $PM_{2.5}$ Exposure and New Onset Asthma in Children

Study	Age Range	Beta Coefficient (SE)
Tetreault et al., 2016	*0-17*	*0.044 (0.0009)*
McConnell et al., 2010	4-17	0.029 (0.017)
Nishimura et al., 2013	7-21	0.030 (0.069)

6.1.4 Cardiovascular Hospital Admissions

Bell et al., 2015 was identified as best characterizing risk across the U.S. for benefits assessment purposes as it included the largest study size, most recent time period, and a nationally representative geographic area. However, it was restricted to ages >64 and based exposure estimates solely on monitoring data. There was also another large study of $PM_{2.5}$-attributable cardiovascular hospital admission impacts that included all ages and incorporated hybrid exposure estimation techniques (Talbott et al., 2014). Differences in the age ranges and ICD-9 codes prevented pooling of the two estimates but comparing the two estimates could provide insights into uncertainties associated with epidemiologic estimates of this health endpoint (Table 40). Therefore, we include a risk estimate of cardiovascular hospital admission impacts from long-term $PM_{2.5}$ exposure from Talbott et al., 2014 as a sensitivity analysis of this health endpoint (Table 41). Please note that Talbott et al., 2014 provides individual risk estimates for each state, which will be pooled into a single estimate to compare with Bell et al., 2015.

Talbott et al., 2014 assessed daily $PM_{2.5}$ concentrations and hospitalizations for cardiovascular disease in Florida, Massachusetts, New Hampshire, New Jersey, New Mexico, New York, and Washington from 2001 to 2008. The authors gathered hospital discharge data from each state's respective data stewards. Talbott et al., 2014 conducted a time-stratified case crossover study using hospitalization data for all cardiovascular diseases (ICD-9 390-459) and for several specific cardiovascular diseases within the ICD-9 390-459 range. Authors used a downscaling Bayesian space-time modeling approach to combine air monitoring data and air gridded numerical outputs from CMAQ to predict daily $PM_{2.5}$ concentrations. The authors gathered meteorological data from the Centers for Disease Control (CDC) Wonder North America Land Data Assimilation System Daily Air Temperatures and Heat Index. Risk estimates were presented for a 10 μg/m^3 increase in $PM_{2.5}$ for each state and season across three single-day lags (0, 1, and 2) and a three-day lag average (0-2) by diagnosis. All-year risk estimates were identified over season-specific estimates and estimates of multiday average lag period were identified over single-day

lag estimates.[80] The seven state-specific risk estimates identified as sensitivity analyses were pooled using the random or fixed effects algorithm in BenMAP-CE.[81] The seven risk estimates reflect a mix of positive and negative values. State-specific risk estimates identified from Talbott et al., 2014 come from a two-pollutant multivariable model including O_3 of ICD-9 codes 390-459: 1.005 (95% CI: 0.998-1.012) for Massachusetts; 1.011 (95% CI: 1.007-1.016) for New Jersey; 1.011 (95% CI: 0.973-1.050) for New Mexico; and 1.011 (95% CI: 1.008-1.014) for New York. Each odds ratio is for a 10 $\mu g/m^3$ increase in the averaged daily mean $PM_{2.5}$ concentration 0-, 1-, and 2-day lags (Talbott et al., 2014, Table 3). Beta effect coefficients from the main (italicized) and sensitivity analyses are available in Table 41.

Table 40. Potential Sensitivity of Estimated Cardiovascular Hospital Admissions

Potential Source of Uncertainty	Potential Insights Gained from Quantitative Uncertainty Analyzes
Application of Risk Estimates to Other Locations and Populations	Talbott et al., 2014 included all ages whereas Bell et al., 2015 was restricted to ages >64
Confounding by Individual Risk Factors (Location)	Talbott et al., 2014 was restricted to seven states, Bell et al., 2015 included all states
Confounding by Other Pollutants	Talbott et al., 2014 included the copollutant O_3
Exposure Estimate	Talbott et al., 2014 used hybrid exposure estimates whereas sever states, Bell et al., 2015 used monitor-based estimates

Table 41. $PM_{2.5}$-Attributable Cardiovascular Hospital Admissions Beta Estimates

Study	Beta Coefficient (SE)
Bell et al., 2015	*0.00065 (0.00009)*
Talbott et al., 2014, MA	MA: 0.00050 (0.00035), NJ: 0.00109 (0.0002), NM: 0.00109 (0.0019), NY: 0.00109 (0.00015), FL: -0.00040 (0.0003), NH: -0.00121 (0.0012) , WA: -0.00090 (0.0005)

6.1.5 Respiratory Hospital Admissions

Similar to cardiovascular hospital admissions, there was an estimate of $PM_{2.5}$-attributable respiratory hospital admissions that included all ages and utilized a hybrid exposure estimation approach, but was geographically limited, in this case to a single state. However, we thought it useful to include this estimate as a sensitivity analysis due to the contrasts between it and the italicized main benefits estimates (Table 42 and Table 43). As compared to $PM_{2.5}$-attributable mortality and cardiovascular hospital admission impact estimates, there may be greater uncertainty associated with estimates of $PM_{2.5}$-attributable respiratory hospital admissions (Table 43).

[80] Lag period preference identification criteria is more fully described in 2019 PM ISA Appendix Table A-1.

[81] Random or fixed effects pooling is a method to combine two or more distributions into a single new distribution, allowing for the possibilities that either 1) a single true underlying relationship exists between the component distributions, and that differences among estimated parameters are the result of sampling error, or 2) the estimated parameter from different studies may in fact be estimates of different parameters, rather than just different estimates of a single underlying parameter, and weights for the pooling are generated via inverse variance weighting, thus giving more weight to the studies that exhibit lower variance and less weight to the input distributions with higher variance.

Jones et al., 2015 encompassed all ages, races, and ethnicities with a case-crossover analysis in New York state, using 24-hour average $PM_{2.5}$ concentrations from CMAQ and meteorological data from the National Climactic Data Center. The authors assessed hospital discharge data from the New York State Department of Health State Planning and Research Cooperative System through principle diagnosis categorized by ICD-9 code (chronic bronchitis (ICD-9 491), emphysema (ICD-9 492), asthma (ICD-9 493), and chronic airway obstruction (ICD-9 496)). Authors used a single pollutant conditional logistic regression model to analyze the respiratory hospital admission and $PM_{2.5}$ chemical constituent data over time and by season. The authors calculated hazard ratios using SAS (version 9.2) with 95% confidence intervals from the regression models. The estimate best characterizing U.S. risk comes from the 4-day lag all-year $PM_{2.5}$ estimate in Figure 2a: 1.006 (1.004-1.009). Please note, this risk estimate was derived from the figure, as the exact numbers were not provided in the paper and the authors did not respond to our request.

Table 42. Potential Respiratory Hospital Admission Sensitivity Insights

Potential Source of Uncertainty	Potential Insights Gained from Quantitative Uncertainty Analyzes[2]
Application of Risk Estimates to Other Locations and Populations	Jones et al., 2015 included all ages whereas Bell et al., 2015 was restricted to ages >64
Confounding by Individual Risk Factors (Location)	Jones et al., 2015 was restricted to a single state, Bell et al., 2015 included all states
Exposure Estimate	Jones et al., 2015 used hybrid exposure estimates, whereas Bell et al., 2015 used monitor-based estimates

Table 43. $PM_{2.5}$-Attributable Respiratory Hospital Admissions Beta Risk Estimates

Study	Age Range	Beta Coefficient (SE)
Bell et al., 2015	*65-99*	*0.00025 (0.0001)*
Ostro et al., 2016	*0-18*	*0.00275 (0.0008)*
Jones et al., 2015	0-99	0.00080 (0.0002)

6.1.5.1 Emergency Hospital Admissions (EHAs)

Interestingly, a substantial subset of the ISA-identified recent epidemiologic literature evaluating respiratory hospitalizations restricted analyses to emergency hospital admissions (EHAs), defined as hospitalizations admitted from the emergency department (section 3.2). Due to time and resource requirements, we were unable to develop county-level baseline incidence data for EHAs, in addition to total hospital admissions. However, as we were interested in how estimates of EHAs compared to total, we include a risk estimate of respiratory EHAs from Zanobetti et al., 2009 using national baseline incidence data. Though the EHA estimate came from a smaller and older study then the main analysis respiratory hospital admission study, the EHA estimate is nearly an order of magnitude larger than the risk estimate included in the main estimate (italicized).

Table 44. Comparison of the $PM_{2.5}$-Attributable Respiratory Hospital Admissions Beta Risk Estimate to the EHA Respiratory Estimate

Study	Beta Coefficient (SE)
Bell et al., 2015	*0.00025 (0.0001)*
Zanobetti et al., 2009	0.00204 (0.0004)

6.1.6 Effect Modification of Health Impacts in At-Risk Populations[82]

ISAs typically include an assessment of the weight of evidence demonstrating that certain subpopulations experience increased mortality or morbidity risks from air pollutant exposure compared to other groups. This is also known as effect modification and occurs when the measure of an effect changes across levels of a variable other than $PM_{2.5}$ exposure. The 2019 PM ISA examined toxicological, controlled human exposures, and epidemiologic literature considering whether certain populations and lifestages might be at increased risk of air pollutant-related health effects (U.S. EPA, 2019c).

The ISAs categorize relationships between exposure and effect modification for various population and lifestages into the following four groups:

- *Adequate* evidence: There is substantial, consistent evidence within a discipline to conclude that a factor results in a population or lifestage being at increased risk of air pollutant-related health effect(s) relative to some reference population or lifestage. Where applicable, this evidence includes coherence across disciplines. Evidence includes multiple high-quality studies.
- *Suggestive* evidence: The collective evidence suggests that a factor results in a population or lifestage being at increased risk of air pollutant-related health effect(s) relative to some reference population or lifestage, but the evidence is limited due to some inconsistency within a discipline or, where applicable, a lack of coherence across disciplines.
- *Inadequate* evidence: The collective evidence is inadequate to conclude whether a factor results in a population or lifestage being at increased risk of air pollutant-related health effect(s) relative to some reference population or lifestage. The available studies are of insufficient quantity, quality, consistency, and/or statistical power to permit a conclusion to be drawn.
- *Evidence of no effect*: There is substantial, consistent evidence within a discipline to conclude that a factor does not result in a population or lifestage being at increased risk of air pollutant-related health effect(s) relative to some reference population or lifestage. Where applicable, the evidence includes coherence across disciplines. Evidence includes multiple high-quality studies.

Presenting $PM_{2.5}$-attributable benefit estimates striated by the value of another covariate can provide insight into risk within various population subgroups. To accomplish this, we reviewed relevant chapters from the 2019 PM ISA in order to compile and assess studies cited in support of the Agency's determinations, focusing on studies referenced in Table 12-3 for population characteristics with either "adequate evidence" (i.e., substantial, consistent evidence) or "suggestive evidence" (i.e., limited

[82] Analyses of effect modification will not be included in the main analyses, so as to avoid the possibility of double-counting impacts. This potential uncertainty could also be described as the effect modification of individual risk factors.

evidence due to inconsistency or a lack of coherence in research) of increased risk (sections 6.1.6.1 and 6.1.6.2) (U.S. EPA, 2019c). The factors with "adequate evidence" for $PM_{2.5}$ are lifestage (children) and race (nonwhite populations), while the factors with "suggestive evidence" are pre-existing disease (cardiovascular disease, respiratory disease, and obesity), genetic factors (variant genotypes), low socioeconomic status, and smoking.

6.1.6.1 Study and Risk Estimate Identification Criteria for Populations At-Risk for $PM_{2.5}$ Exposures

We identified all studies in the related section of ISA Chapter 12 for each at-risk factor listed above, resulting in a set of 123 studies for at-risk populations. This collection includes the following number of studies, with some studies duplicated for multiple endpoints.

- 8 studies for lifestage (children),
- 25 studies for race (nonwhite populations),
- 67 studies for pre-existing disease across disease types,
- 18 studies for genetic factors, 25 studies for socioeconomic status, and
- 14 studies for smoking.

We then focused our review on the risk factors with "adequate evidence", due to stronger supporting evidence as well as because they could be evaluated using currently available data. We extracted study information from all studies with "adequate evidence" and applied initial screening criteria to identify peer-reviewed, epidemiological studies focused on $PM_{2.5}$ conducted in the US or Canada. We also documented the mortality and/or morbidity health endpoints included in each study, focusing on all-cause mortality and respiratory morbidity endpoints. We then evaluated the group of remaining studies based on additional identification criteria built off the criteria for the primary analysis, described in Table 45.

Table 45. $PM_{2.5}$ At-Risk Study Identification Criteria

Criterion	**Notes**
Peer-Review	Peer-reviewed research exclusively
Study design	Epidemiological study
$PM_{2.5}$ Study	$PM_{2.5}$ exposure rather than other PM_{10} or other sizes
Study Location	US or Canada
Study Duration	Long-term studies preferred
Population Attributes	Presents risk estimates for clearly defined at-risk groups for which data currently exist in BenMAP-CE
Causal or Likely Causal Health Effects	Adequate evidence for at-risk groups in ISA
Economically Valuable Health Effects	Health endpoints for which economic values have been or could reasonably be developed
Baseline Incidence Data	Must be able to identify baseline incidence data for subpopulations

6.1.6.2 All-Cause Mortality

For the mortality endpoint, seven all-cause mortality studies for the nonwhite population met our criteria. No mortality studies for the child at-risk group met the initial screening criteria. Of the seven studies of nonwhite populations, three were short-term exposure studies relating daily $PM_{2.5}$ exposure

and daily deaths and four were long-term exposure studies relating annual $PM_{2.5}$ exposure and annual mortality. Consistent with the main benefits assessment, we focused on the following four long-term studies as long-term exposure studies may include some effects of short-term exposures (section 2.2.5.1): Di et al., 2017b, Kioumourtzoglou et al., 2016, Parker et al., 2018, and Wang et al., 2017.

We evaluated specific details of risk estimates provided by each study to determine if sufficient information exists for use in a quantitative sensitivity analysis. Of the studies, only Di et al., 2017b provided sufficient information to apply risk models quantifying increased risks to nonwhite groups, including non-Hispanic white, Black, Asian, Native American, and Hispanic-white populations. Additional detail on the study can be found in section 2.2.5.1.3.1.2 or in the associated Study Information Table.

We applied similar criteria to morbidity endpoints for the child and nonwhite at-risk groups. No studies cited for the child subgroup met our criteria for inclusion, and one endpoint, emergency room visits for asthma, was chosen for quantification for the nonwhite populations at-risk factor group. The study we chose to evaluate was Alhanti et al., 2016, which presents risk information for white and pooled nonwhite populations disaggregated into five age groups.

We developed BenMAP-ready Health Impact Functions for each at-risk group described by Di et al., 2017b and Alhanti et al., 2016, summarized in Table 46.

Table 46. Identified $PM_{2.5}$ At-Risk Beta Coefficients and Standard Errors

At-Risk Factor	**Endpoint**	**Study**	**Subgroup**	**Beta Coefficient (SE)**
Race, nonwhite populations	Morality, All Cause	Di et al., 2017b	Non-Hispanic White	0.0061 (0.0001)
			Hispanic White	0.0110 (0.0008)
			Black	0.0189 (0.0004)
			Asian	0.0092 (0.0010)
			Native American	0.0095 (0.0019)
Race, nonwhite populations	Emergency Room Visits, Asthma	Alhanti et al., 2016	White, age 0-4	0.0025 (0.0019)
			Nonwhite, age 0-4	0.0037 (0.0012)
			White, age 5-18	0.0025 (0.0016)
			Nonwhite, age 5-18	0.0049 (0.0012)

6.2 Quantitative Characterization of O_3 Uncertainties and Evaluating Sensitivity to Alternate O_3 Assumptions

6.2.1 Statistical Uncertainty Around the Risk Estimate (Monte-Carlo Assessment)

For all endpoints analyzed, we use a Monte Carlo simulation in which we sample from the standard error associated with each risk estimate and present the resulting 2.5th and 97.5th percentile values from this distribution as a 95th percentile confidence interval around the estimated health impact and monetized health benefits. Monte Carlo methods are a well-established means of characterizing random sampling error associated with the risk estimates from epidemiologic studies. This approach randomly samples from a distribution of incidence and valuation estimates to characterize the effects of uncertainty on output variables. The reported standard errors in the epidemiologic studies determined the distributions for individual effect estimates for endpoints estimated using a single study. For endpoints estimated using a pooled estimate of multiple studies, the confidence intervals reflect both the standard errors and the variance across studies. The confidence intervals around the monetized benefits incorporate the standard errors from the epidemiologic risk estimate as well as the distribution of the valuation function. These confidence intervals do not reflect other sources of uncertainty inherent within the estimates, such as baseline incidence rates, populations exposed and transferability of the effect estimate to diverse locations. As a result, the reported confidence intervals and range of estimates give an incomplete picture about the overall uncertainty in the benefits estimates.

6.2.2 Respiratory Mortality

6.2.2.1.1 Confounding by $PM_{2.5}$

When considering the relationship between pollutant exposure and health impacts, it can be informative to consider whether risk estimates are changed when other pollutants are included in copollutant models, especially when health impacts of multiple pollutants are being estimated concurrently. While no conclusions were formed regarding the impact of copollutant confounding on long-term exposure-related respiratory mortality, the 2020 O_3 ISA found that "positive associations observed between long term O_3 exposure and total mortality remain relatively unchanged after adjustment for $PM_{2.5}$ and NO_2."

Turner et al., 2016 provided single- and multipollutant (including $PM_{2.5}$ as a copollutant) O_3-attributable respiratory mortality risk estimates. A comparison of risk estimates that either do or do not include $PM_{2.5}$ as a copollutant is included to clarify this potential sensitivity with respect to O_3-attributable respiratory mortality. Differences in the magnitude of risk estimates including or excluding $PM_{2.5}$ as a copollutant are provided in Table 47.

Table 47. Single- and Two-Pollutant (Including $PM_{2.5}$ as a Copollutant) Long-Term O_3-Attributable Respiratory Mortality Risk Estimates per 10 ppb

Study	Single-Pollutant	Multipollutant
Turner et al., 2016	1.14 (1.10-1.18)	1.12 (1.08-1.16)

6.2.2.2 Short-Term O_3 Exposures

6.2.2.2.1 Potential Threshold Analysis

The 2020 final O_3 ISA evaluated a number of studies examining the shape of the concentration-response relationship for short-term O_3 exposure and total/nonaccidental mortality, which we use to inform the long-term O_3-attributable respiratory mortality relationship. The ozone ISA found that "studies that used different statistical approaches and ozone averaging times (i.e., 24 hour avg and 8 hour max) provide evidence of a linear concentration-response relationship, with less certainty in the shape of the curve at lower concentrations [i.e., …30 ppb for 8 hour max], [although] an examination of whether a threshold exists in the ozone mortality concentration-response relationship provided no evidence of a concentration below which mortality effects do not occur when examining 5 μg/m^3 (~2.55 ppb) increments across the range of 1 hour max concentrations reported in the U.S. and Canadian cities included in [a large cohort]." As the Zanobetti and Schwartz, 2008 risk estimate uses the MDA8 metric, it can be used to quantitatively assess the effect of an O_3 threshold at 30 ppb would have on benefits estimates. For context, approximately 3.7% of the contiguous U.S. population is projected to reside in areas where MDA8 O_3 concentrations are annually below 30 ppb in 2024 (U.S. EPA, 2020b). Clinical evidence provides little indication that adverse effects occur at extremely low levels in most individuals. Epidemiologic evidence is qualitatively discussed further in section 6.5.14.2.

6.2.2.2.2 Confounding by PM

Regarding short-term exposures, the 2020 O_3 ISA found that "the few recent multicity studies that examined potential copollutant confounding provide evidence supporting that O_3 mortality risk estimates are relatively unchanged or slightly attenuated, but remain positive, in copollutant models with $PM_{2.5}$, PM_{10}, and NO_2."

Katsouyanni et al., 2009 provided single- and two-pollutant (including PM_{10} as a copollutant) short-term O_3-attributable respiratory mortality risk estimates for a subset of 15 of the 86 cities analyzed. A comparison of risk estimates that either do or do not include PM_{10} as a copollutant is included to clarify this potential sensitivity with respect to O_3-attributable respiratory mortality. Differences in the magnitude of risk estimates including or excluding $PM_{2.5}$ as a copollutant are provided in Table 48. Please note, as distributed lag risk estimates were not provided for the two-pollutant analyses, in additional to the inclusion of $PM_{2.5}$ as a copollutant and the number of cities analyzed, there is a difference in the lag duration between the estimates in Table 48.

Table 48. Single- and Two-Pollutant (Including PM_{1o} as a Copollutant) Short-Term O_3 Exposure O_3-Attributable Excess Premature Respiratory Mortality Risk Estimates per 10 ppb

Study	Single-Pollutant	Two-Pollutant
Katsouyanni et al., 2009	0.77% (0.17%, 1.37%)	0.99% (-0.33%, 2.31%)

6.2.3 All-Cause Mortality

When estimating air pollutant-attributable health impacts, EPA focuses on endpoints for which the underlying scientific evidence is strongest. That is, when evaluating evidence across scientific disciplines (i.e., clinical, animal toxicological, and epidemiologic) there is often consistency of effects within a discipline, coherence of effects across disciplines, and evidence of biological plausibility. Such an approach gives us greater confidence in the relationship between exposure and health outcome. For

criteria pollutants, EPA typically relies upon the causality determinations in the latest ISA or equivalent, which are made using a weight-of evidence approach. Generally, to estimate the pollutant-attributable human health benefits in which we are most confident, we at least assess health effects identified as having a 'causal' or 'likely to be causal' relationship with the pollutant of interest in the most recently published ISA. This is not to imply there may not be benefits associated with endpoints having a "suggestive of, but not sufficient to infer, a causal relationship," but rather that there is greater uncertainty in these potential benefits.

Because of the significance of the endpoint, we include a limited quantitative sensitivity analysis of total mortality associated with long-term O_3 exposure. While the 2020 O_3 ISA concluded that evidence was "suggestive of, but not sufficient to infer," a causal relationship between long-term exposures and total mortality, the reduction of this risk is likely still valuable to society. As such, for this sensitivity discussion, we include risk estimates of long-term, all-cause O_3-attributable total mortality from the two studies used to estimate $PM_{2.5}$-attributable mortality risk (Table 49). Please note these long-term, all-cause risk estimates include respiratory mortality estimates and should not be added to the respiratory mortality estimates.

Table 49. Long-Term O_3-Attributable Total Mortality Risk Estimates per 10 ppb

Study	**Risk Estimate (per 10 ppb increase in O_3)**	**Risk Estimate Details**
Turner et al., 2016	1.02 (1.01-1.03)	Fully adjusted HBM multipollutant estimate from Table E9, ages 35-99
Di et al., 2017b	1.011 (1.010, 1.012)	GEE two-pollutant main analysis estimate from Table 2, ages 65-99

6.2.4 Asthma Onset in Children

The study identified as best characterizing risk for asthma onset in children was conducted in Canada (Tetreault et al., 2016). Even though comparatively Tetreault et al., 2016 was preferred in identification criteria to other available studies (e.g., study size, exposure estimation technique, etc.) other than location and study period, we thought it useful to include the largest and most recent U.S.-based risk estimates as a sensitivity analysis. An overall comparison of the main risk estimate from Tetreault et al., 2016 and the alternative risk estimates from Garcia et al., 2019 can be found in Table 50. Details about the study providing an alternate risk estimate is below.

Table 50. Potential Sensitivity of Estimated Instances of Asthma Onset

Potential Source of Uncertainty	Potential Insights Gained from Quantitative Uncertainty Analyses[2]
Application of Risk Estimates to Other Locations and Populations	Tetreault et al., 2016 included only Canadians whereas Garcia et al., 2019 was restricted to southern CA
Study Size	Tetreault et al., 2016 included the largest study size, approximately twenty-five times the size of Garcia et al., 2019
Study Period	Garcia et al., 2019 evaluated a more recent and longer health study period (1993-2014) compared to 2002-2011 for Tetreault et al., 2016
Exposure Estimate	Tetreault et al., 2016 used hybrid exposure estimates whereas sever states, whereas Garcia et al., 2019 used monitor-based estimates
Statistical Technique	Tetreault et al., 2016 used time-varying Cox proportional hazard models, whereas Garcia et al., 2019 uses Poisson log-linear regression models

Three of the four ISA-identified studies of long-term O_3-attributable asthma onset took place in the U.S., although only one included a study period more recent than 2005 (Garcia et al., 2019). Garcia et al., 2019 examined the associations between long-term ozone exposure and asthma onset in children (aged nine-18 years) with no history of asthma in Southern California. The authors followed three waves of participants from the Children's Health Study for eight years between 1993 and 2014. Garcia et al., 2019 obtained health and demographic data from parents, guardians, or participants, who completed questionnaires annually. In order to calculate annual mean, community-level ozone exposure, the authors acquired daily eight-hour mean O_3 concentrations through ambient air pollution monitors. Multi-level Poisson regression models with one-year lag showed no statistically significant associations between long-term O_3 exposure and asthma onset in children. Models adjusted for demographic variables as well as factors pertaining to family medical history, environmental factors, and near-roadway pollution.

The magnitudes of main and alternate risk estimates of long-term O_3 exposure and asthma onset in children provided in Table 51.

Table 51. Long-Term O_3-Attributable Asthma Beta Coefficients

Study	Beta Coefficient	Age Range
Tetreault et al., 2016	*0.020754*	*0-17*
Garcia et al., 2019	0.01695	9-18

6.2.5 Understanding the Effect Modification of Health Impacts in At-Risk Populations[83]

Effect modification was also investigated with regard to O_3 exposures. We reviewed relevant chapters from 2020 O_3 ISA and used a similar methods to that described for $PM_{2.5}$ to compile and assess studies cited in support of the Agency's determinations (section 6.1.6). As the 2020 O_3 ISA only presents an evaluation of at-risk groups in summary form and extensively references the findings from the 2013 O_3 ISA, we focused on the detailed chapter from that previous document in identifying the at-risk factors and studies to review (U.S. EPA, 2013).Factors with "adequate evidence" are genetic factors, asthma, children, older adults, diet, and outdoor workers. Factors with "suggestive evidence" are sex, SES, and obesity. Considering feasibility and our review criteria, we focused on studies addressing increased risks based on age in the adequate evidence group and note that some health functions already applied in the primary analysis focus on asthmatic subpopulations. We also elected to include illustrative calculations for some risk factors with "suggestive evidence", specifically those for sex.

6.2.5.1 Study and Risk Estimate Identification Criteria for Populations At-Risk for O_3 Exposures

We compiled epidemiologic studies from the related section of Chapter 8 of the 2013 O_3 ISA for the following at-risk factors, excluding all other study types (e.g. toxicological studies), for a total of 28 studies. This collection includes the following number of studies, with some studies duplicated for multiple endpoints.

- 9 studies for children,
- 10 studies for older adults, and
- 18 studies for sex

We excluded the genetic factors population from our analysis, as we do not currently have the capability to estimate health impacts among variant genotypes. We excluded diet, outdoor workers, and obesity for similar reasons, as we have no representative dataset for use in analysis with these risk factors. Effects on asthmatics were not included in this analysis because we currently lack highly resolved spatial data on asthma prevalence, in part because effects on asthmatic populations are included in the main analysis.[84] We also excluded the SES group as the studies associated with the SES group for O_3 were associated with other methodological challenges. We coded the identified studies into a spreadsheet and applied the initial screening criteria described previously. We collected information on mortality and/or morbidity endpoints assessed in each study and focused on all-cause mortality and respiratory morbidity endpoints. The remaining studies were evaluated based on the additional identification criteria described in Table 52.

[83] Analyses of effect modification will not be included in the main analyses, so as to avoid the possibility of double-counting impacts. This potential uncertainty could also be described as the effect modification of individual risk factors.

[84] Effects on asthmatics using national level prevalence estimates are estimated in the main analysis.

Table 52. O_3 At-Risk Study Identification Criteria

Criterion	Notes
Peer-Review	Peer-reviewed research exclusively
Study Design	Epidemiologic study
Ozone Study	Research on ozone exposure is used
Study Location	U.S. or Canada
Population Attributes	Presents risk estimates for clearly defined at-risk groups for which data currently exist in BenMAP-CE
Exposure Duration	Both short- and long-term exposure studies
Causal or Likely Causal Health Effects	Adequate or suggestive evidence for at-risk groups in ISA
Economically Valuable Health Effects	Health endpoints for which economic values have been or could reasonably be developed
Baseline Incidence Data	Must be able to identify baseline incidence data for subpopulations
Season	All year exposure or warm season exposure
Ozone Exposure Metrics	MDA8, or able to be converted to MDA8
Lag Structure	Choose model that most clearly represents the relationship between ozone exposure and the physiologic changes for the health endpoint

6.2.5.2 Total Mortality

Regarding the health endpoint of mortality, three studies for older adults met our criteria: Medina-Ramon and Schwartz, 2008, Zanobetti and Schwartz, 2008, and Katsouyanni et al., 2009. All three studies provided sufficient details to apply risk model information for short-term all-cause mortality among adult age groups.[85] There were no mortality studies for the child at-risk group in either the 2013 or 2020 O_3 ISAs (U.S. EPA, 2013, U.S. EPA, 2020a). For the at-risk population stratified by sex, two studies met our initial criteria: Medina-Ramon and Schwartz, 2008, which evaluated short-term O_3 exposure and all-cause mortality, and Jerrett et al., 2009, which evaluated long-term O_3 exposure and respiratory mortality. Both studies provided sufficient data to apply risk model information to male and female subpopulations. We developed health impact functions for these studies.

The O_3-mortality risk estimates for at-risk subpopulations reported in Medina-Ramon and Schwartz, 2008 required additional modification in order to use those results to develop health impact functions. The authors presented excess risk estimates for each subpopulation as the additional percent change in mortality for persons who have the condition, compared to persons without the condition. For our populations of interest, these subgroups were persons age 65 or older compared to those younger than 65, and females relative to males. However, they did not report the risk estimate for these comparison groups, so in order to estimate the total excess risk for each exposed at-risk group, we needed to first back-calculate the excess risk for the comparison group without the factor of interest. We accomplished this by assuming that the authors' overall reported excess risk for the full sample of 0.65% (95% confidence interval = 0.38% to 0.93%) could be expressed as a weighted average of the unreported excess risk ("x") and the full excess risk for the at-risk group, which would be expressed as the sum of x

[85] Calculations required to apply risk model information from Medina-Ramon and Schwartz, 2008 are described in the following paragraph.

and the reported excess risk from Medina-Ramon and Schwartz, 2008 Table 2, where the weights are calculated using the total and at-risk group sample sizes in Table 1 of that paper. For example, to calculate the total excess risks for the females in the sample, we used the following equation:

$$\mathrm{ER}_{\mathrm{Total}} = \frac{\mathrm{ER}_{\mathrm{Male}}(\mathrm{Pop}_{\mathrm{Male}}) + \mathrm{ER}_{Female}(\mathrm{Pop}_{\mathrm{Female}})}{\mathrm{Pop}_{\mathrm{Total}}}$$

where ER_{Total} is the full sample excess risk of 0.65%; ER_{Female} is the excess risk of ozone exposures for females; ER_{Male} is the excess risk of ozone exposures for males; Pop_{Total} is the total sample population; and Pop_{Female} and Pop_{Male} are the size of the female and male subsets of the sample population, respectively. We also know from Table 2 of that paper that:

$$\mathrm{ER}_{\mathrm{Female}} = \mathrm{ER}_{\mathrm{Male}} + 0.58\ \%$$

Substituting and using the available information from Medina-Ramon and Schwartz, 2008 Tables 1 and 2, we can solve for ER_{Male} and then ER_{Female}:

$$0.65\% = \frac{\mathrm{ER}_{\mathrm{Male}}(1{,}365{,}937) + (0.58\% + \mathrm{ER}_{\mathrm{Male}})(1{,}363{,}703)}{2{,}729{,}640}$$

$$\mathrm{ER}_{\mathrm{Male}} = 0.36\ \%$$

and

$$\mathrm{ER}_{\mathrm{Female}} = 0.36\% + 0.58\% = 0.94\%$$

We then used the full excess risk value for the female subpopulation to derive a health impact function for ozone-related mortality for females.

6.2.5.3 Respiratory Morbidity

We applied the same identification criteria described in section 6.2.5.1 to respiratory morbidity endpoints for the child and sex at-risk groups. Three studies for children met our criteria for inclusion: Mar and Koenig, 2009, Paulu and Smith, 2008, and Villeneuve et al., 2007. Each study evaluated emergency room visits for asthma and provided sufficient risk model information stratified by age. No studies cited for the older adult population met our criteria for inclusion. Three studies for sex met our identification criteria: Paulu and Smith, 2008, Cakmak et al., 2006, and Lin et al., 2005. These studies evaluated emergency room visits for asthma, all respiratory hospital admissions, and hospital admissions for lower respiratory infection, respectively. Each study provided sufficient risk model information for male and female subpopulations. We developed health impact functions for all studies identified above. All the at-risk studies we identified are summarized in Table 53.

Table 53. Identified O_3 At-Risk Beta Coefficients and Standard Errors

At-Risk Factor	Endpoint	Study	Subgroup	Beta Coefficient (SE)[1]
Lifestage, older adults	Mortality, All Cause	Medina-Ramon and Schwartz, 2008 and Zanobetti and Schwartz, 2008	Age 0-64	-0.0001 (0.0001)
			Age 65+	0.0010 (0.0002)
Lifestage, older adults	Mortality, All Cause	Katsouyanni et al., 2009	Age 0-74	0.0008 (0.0002)
			Age 75+	0.0007 (0.0003)
Lifestage, older adults	Mortality, All Cause	Zanobetti and Schwartz, 2008	Age 0-20	0.0001 (0.0003)
			Age 21-30	0.0001 (0.0004)
			Age 31-40	0.0001 (0.0002)
			Age 41-50	0.0001 (0.0002)
			Age 51-60	0.0005 (0.0002)
			Age 61-70	0.0004 (0.0001)
			Age 71-80	0.0005 (0.0001)
			Age 81+	0.0003 (0.0001)
Sex	Mortality, All Cause	Medina-Ramon and Schwartz, 2008 and Zanobetti and Schwartz, 2008	Female	0.0009 (0.0002)
			Male	0.0004 (0.00004)
Sex	Mortality, Respiratory	Jerrett et al., 2009	Female	0.0044 (0.0011)
			Male	0.0011 (0.0014)
Lifestage, children	Emergency Room Visits, Asthma	Mar and Koenig, 2009	Age 0-17	0.0104 (0.0044)
			Age 18+	0.0039 (0.0027)
Lifestage, children	Emergency Room Visits, Asthma	Paulu and Smith, 2008	Age 2-14	0.0104 (0.0050)
			Age 15-34	0.0148 (0.0035)
Lifestage, children	Emergency Room Visits, Asthma	Villeneuve et al., 2007	Age 2-4	0.0032 (0.0033)

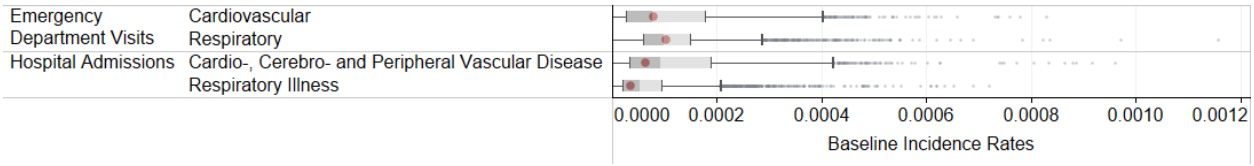
			Age 5-14	0.0073 (0.0024)
			Age 15-44	0.0058 (0.0018)
			Age 45-64	0.0063 (0.0033)
			Age 65-74	0.0073 (0.0055)
			Age 75+	-0.0006 (0.0067)
Sex	Emergency Room Visits, Asthma	Paulu and Smith, 2008	Female	0.0113 (0.0027)
			Male	0.0104 (0.0032)
Sex	Hospital Admissions, All Respiratory	Cakmak et al., 2006	Female	0.0013 (0.0004)
			Male	0.0017 (0.0003)
Sex	Hospital Admissions, Lower Respiratory Infection	Lin et al., 2005	Female	0.0087 (0.0060)
			Male	0.0040 (0.0052)

[1] Beta coefficients and SEs in this table have been converted to MDA8 for comparability

6.3 Quantitative Characterization of Baseline Incidence Rate Uncertainties

When available from HCUP, we incorporate county-level hospital admissions and emergency department visit baseline incidence data. Comparisons of the county-level data (box and whisker plot) to the national-level data (red circles) are available in Figure 14.

Figure 14. Example County-Level and National-Level Emergency Department Visit and Hospital Admission Baseline Incidence Data



We performed several quality assurance checks to ensure the incidence rates accurately reflect observed health outcomes in the underlying counties. These checks included:

- Examining data inputs to ensure the endpoints reflect the specified set of ICD codes from the epidemiological studies;
- Reviewing data processing scripts to ensure all calculations implement the intended procedures, as documented in the BenMAP-CE User Manual (U.S. EPA, 2018);
- Re-processing existing incidence rates in BenMAP-CE's "Other Incidence (2014)" to confirm that changes to data processing to incorporate new endpoints have no or minimal impact on incidence rate data for existing endpoints from BenMAP-CE's 2017 data update;

- Comparing the relative magnitude of related endpoints to ensure that incidence rates for broader endpoints (e.g., HA, All Respiratory) are greater than incidence rates for endpoints with a narrower set of ICD codes (e.g., HA, Asthma);
- Comparing national baseline incidence counts when using county-level incidence rates and nation-level incidence rates to ensure that, in aggregate, the two datasets produce similar results;[86] and
- Examining the geographic distribution of incidence rates to ensure no counties, states, or regions, are characterized by anomalously low or high incidence.

We identified no systematic errors or bias in the raw data or data processing steps. The main source of uncertainty in these data is related to imputation of rates where county data for specific endpoints were suppressed due to statistical reliability or privacy concerns. The state or regional rates used to substitute for these suppressed values may under- or over-estimate individual county rates.

6.4 Quantitative Characterization of Economic Valuation Estimate Uncertainties

6.4.1 Mortality Cessation Lag

Following advice from the Health Effects Subcommittee of EPA's independent Science Advisory Board (SAB-HES), the agency typically assumes that some amount of time lapses between when air pollution is reduced and when PM-attributable mortality is reduced fully. Within the context of benefits analyses, this term is often referred to as "cessation lag." The duration of this lag affects how changes in PM-attributable mortality associated with long-term (i.e., years-long) exposure are valued. Economic theory suggests that the value of these future impacts should be discounted. The primary analysis included in recent RIAs assumes that this lag is distributed over a 20-year period, with 30% of deaths reduced in year 0, 50% occur in years 1-5, and the remaining 20% occur in years 6-20. This approach is generally support by SAB recommendations (Cameron, 2001, Cameron, 2004, Hammitt and Bailar, 2010).

Based on SAB requests and recommendations, we previously performed several quantitative uncertainty analyses with the goal of better understanding potential impacts of different cessation lag distribution assumptions (U.S. EPA, 2012b). Although it was determined that certain extreme lag structure assumptions may substantially impact monetized benefits, potentially increasing or decreasing monetized impacts by up to 25%, for most reasonable distributed lag model structures, differences in the specific shape of the lag function had relatively small impacts on overall $PM_{2.5}$ benefits estimates.

We do not know how long-term O_3 exposure-related respiratory deaths are distributed over time. Hence, when discounting the value of O_3-attributable deaths we use two lag structures originally developed for $PM_{2.5}$ (the 20-year segmented lag used for $PM_{2.5}$ and an assumption of zero lag) as sensitivity analyses.

6.4.2 Lung Cancer Cessation Lag

For a given health effect attributable to air pollution exposure, EPA reports the number of avoided cases associated with the estimated pollutant reduction in a specified year. However, for some health effects, there is an expected time lag between changes in pollutant exposure in a given year and the total realization of health effect benefits, commonly referred to in regulatory analyses as the "cessation lag"

[86] Aggregated county-level baseline incidence counts for all hospitalization and emergency department visit endpoints included in the main benefits estimates were within 10% of the national baseline incidence counts.

(section 6.4.1). For an outcome such as lung cancer, where the time between exposure and diagnosis can be quite long, it may take decades to realize the full benefits of the air quality improvements. Properly estimating the time course over which lung cancer health benefits are realized is critical for proper discounting of the economic value of these health benefits.

Following guidance from EPA's Science Advisory Board (Ostro, 2004, EPA RIAs have applied a 20-year distributed cessation lag model to estimate the temporal distribution of reductions in mortality risks, including fatal lung cancer cases. In the 20-year distributed lag model, 30 percent of the total mortality risk reductions occur in the first year following the exposure reduction, 50 percent are distributed evenly among years two through five, and the remaining 20 percent are distributed evenly among years six through 20. This structure reflects mortality risks from a variety of causes, with the mortality risk reductions occurring later representing mortality risks from lung cancer.

For non-fatal cancer incidence, we considered a similar cessation lag approach based on estimates of the lung cancer "latency period," or the time that passes between exposure and diagnosis, when diseases processes may be occurring undetected and not yet resulting in observable symptoms. Based on findings in the 2019 PM ISA, EPA has recently developed a health impact function based on Gharibvand et al., 2017 for non-fatal lung cancer incidence. To support the new non-fatal lung cancer risk estimate, we applied an age-at-diagnosis cessation lag distribution for the main analysis as it accounts for age-specific latency period, instead of assuming a single latency duration. However, other potentially applicable distribution models are available that also take into account the latency between exposure and lung cancer diagnosis, such as the adapted 20-year distribution (section 6.4.2.1) and the latency-based triangular distribution (section 6.4.2.2). All potential lag cessation distributions, including the traditional 20-year lag distribution, are compared in section 6.4.2.3.

6.4.2.1 Adapted 20-Year Distribution

We adapted the 20-year distributed lag model applied to VSL estimates in previous EPA RIAs using the estimated 10-year latency period. Following the latency period, the adapted 20-year model has zero cancer case reductions in years one through five and an even distribution of case reductions in years six through 20, resulting in scaling factors of 0.71 for a 3% discount rate or 0.46 for a 7% discount rate.

6.4.2.2 Latency-Based Triangular Distribution

A continuous probability distribution shaped like a triangle may better assess lung cancer lag cessation. Triangular distribution based on a search of lung cancer latency periods from the peer-reviewed literature. Using the most common latency period of 10-years observed in the literature (Table 29), we estimated a triangular distribution that spans from five to 20 years, with the peak of the distribution at ten years, the most common latency period estimate found in the literature (i.e., the mode). We identified a triangular distribution to reflect the uncertainty of latency period duration found in the literature, given the limited amount of information available to establish the shape and form of an uncertainty distribution. We used the cumulative probability function for this distribution to estimate the incremental annual number of cases likely to be diagnosed year to year by subtracting the cumulative probability from the previous year from the cumulative probability of the current year. We then used the resulting percentages to create a cessation lag model, allocating cases avoided in the years following an exposure change according to the corresponding yearly percentages.

6.4.2.3 Comparison of Lung Cancer Lag Cessation Distribution Models

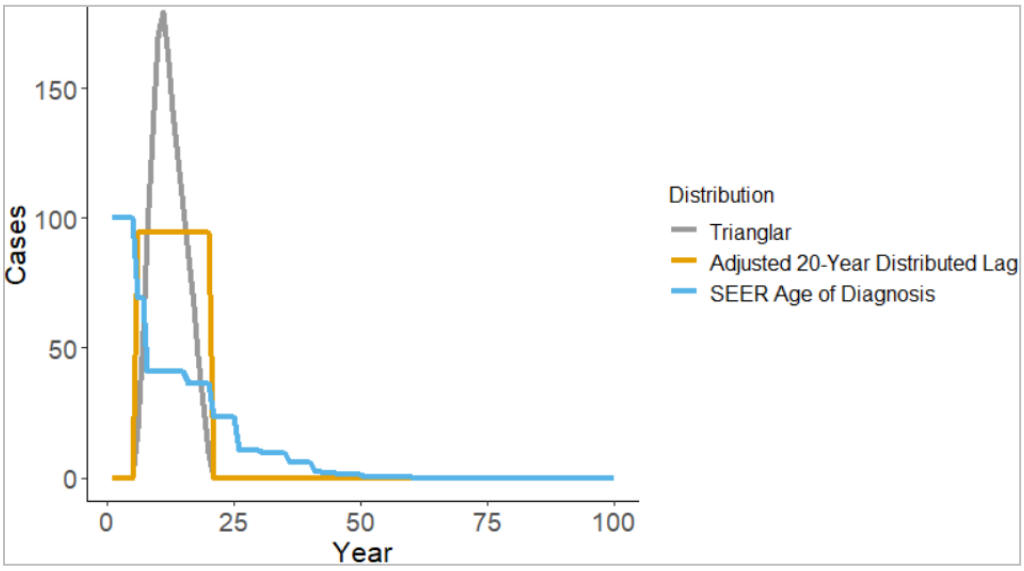
The effect of each potential cessation lag distribution model was converted into scaling factors (Table 54). The scaling factors of the adjusted 20-year lag distribution estimate falls between that of the traditional cessation lag and the triangular distribution lag estimates. Also, the adjusted cessation lag distribution underestimates as compared to the age-at-diagnosis distribution.

Table 54. Scaling Factors for Various Lung Cancer Lag Cessation Distribution Models

Discount Rate	Age Range	Scaling Factor	Lag Cessation Distribution Model
3%	65-99	0.668980939	Traditional VSL cessation lag, 3% DR
7%	65-99	0.398456232	Traditional VSL cessation lag, 7% DR
3%	30-99	0.70711338	Adjusted 20-Year Distributed Lag Adjustment Factor
7%	30-99	0.463225599	Adjusted 20-Year Distributed Lag Adjustment Factor
3%	30-99	0.72192703	Triangular Adjustment Factor
7%	30-99	0.480176715	Triangular Adjustment Factor
3%	30-34	0.350285148	SEER Age-Distribution Adjustment Factor
3%	35-44	0.427591186	SEER Age-Distribution Adjustment Factor
3%	45-54	0.553445022	SEER Age-Distribution Adjustment Factor
3%	55-64	0.675599356	SEER Age-Distribution Adjustment Factor
3%	65-74	0.775053763	SEER Age-Distribution Adjustment Factor
3%	75-84	0.843760064	SEER Age-Distribution Adjustment Factor
3%	85-99	0.916741635	SEER Age-Distribution Adjustment Factor
7%	30-34	0.108397669	SEER Age-Distribution Adjustment Factor
7%	35-44	0.168901798	SEER Age-Distribution Adjustment Factor
7%	45-54	0.294643444	SEER Age-Distribution Adjustment Factor
7%	55-64	0.445786107	SEER Age-Distribution Adjustment Factor
7%	65-74	0.590393871	SEER Age-Distribution Adjustment Factor
7%	75-84	0.702750875	SEER Age-Distribution Adjustment Factor
7%	85-99	0.82379138	SEER Age-Distribution Adjustment Factor

Using the lung cancer incidence risk estimates and a hypothetical scenario, we compared the three potential lung cancer cessation lag models. The annual reduction in cancer cases was estimated from zero to 100 years after the exposure change. For the triangular and adjusted 20-year distributed lag, all annual reductions occur within 20 years after exposure change and for the age of diagnosis distribution, all annual reductions fall within 67 years after exposure change (Figure 15) with 90% occurring by year 26.

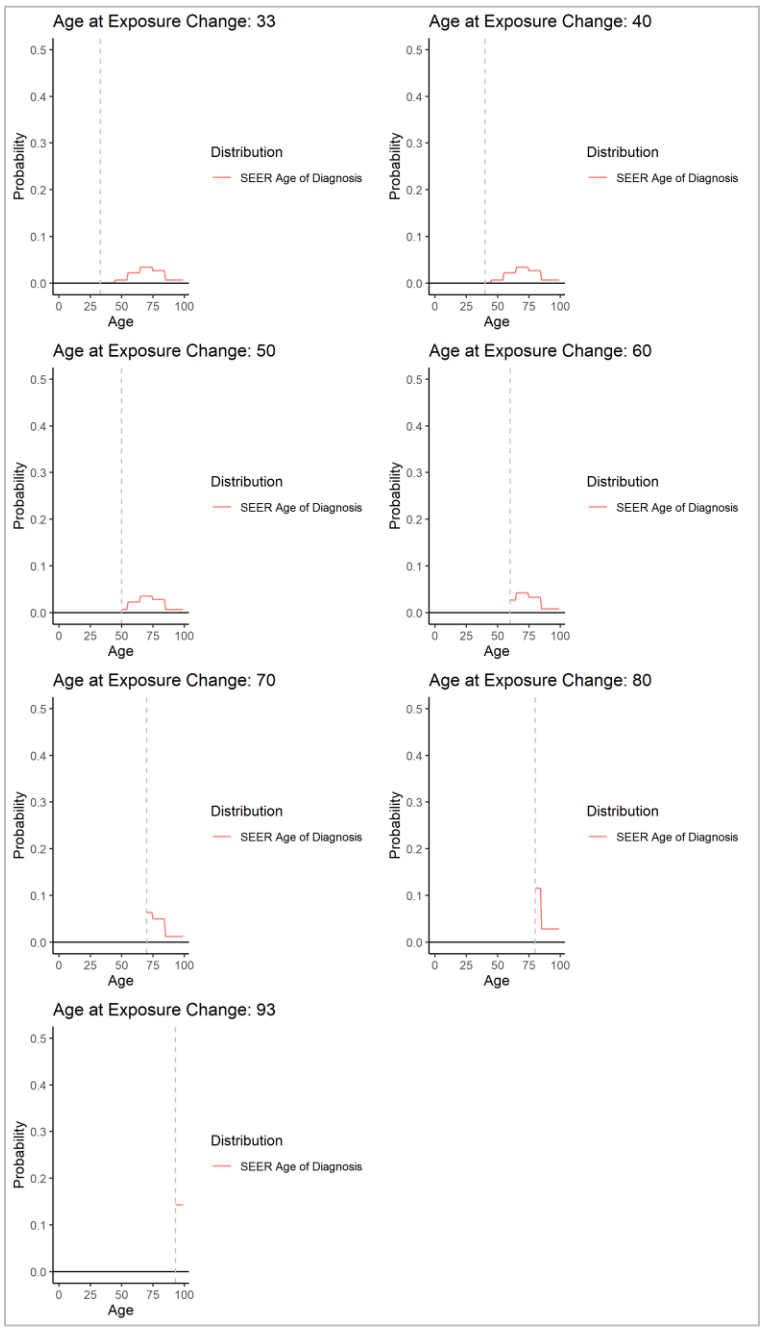
Figure 15. Lung Cancer Cases Cessation Lag Distribution by Model



A potential limitation of the triangular distribution and adjusted 20-year distributed lag is that the same latency period is used for all ages. For an exposure change experienced at 30, both the triangular distribution and adjusted 20-year distributed lag estimate that reductions occur between ages 35 and 50. However, SEER data indicates that less than 5% of lung and bronchus cancer diagnoses occur during this period. Conversely, for an exposure change experienced at 90, the reductions are realized from ages 95 to 110 (greater than life expectancy).

A limitation of the age-of-diagnosis distribution methods is that the highest reductions occur in the first five years for the age-of-diagnosis distribution and not all ages display latency periods (Figure 15). The factor used in this method estimates the time pattern of benefits based on the percentage of cancer incidence remaining in the life and results in older age bins without latency periods (Figure 16). While an age-dependent latency period may more accurately reflect the diagnosis data, the age-of-diagnosis distribution method may overestimate case reductions in earlier years by assuming all reduced cases for a change in exposure at later ages are realized by the end of life (age 99). At the same time, some cases are delayed by two to five decades, beyond latency values reported in the literature for lung cancer.

Figure 16. Lung Cancer Cases Reduction Distribution



6.4.3 Income Elasticity of Willingness to Pay

The degree to which one's WTP to reduce the risk of adverse effects changes in proportion to future changes in income is uncertain. We previously evaluated the potential impact of this factor on the monetized benefits in a sensitivity analysis (U.S. EPA, 2012b). Results are available below.

Our estimates of monetized benefits account for growth in real gross domestic product per capita by adjusting the WTP for individual endpoints based on the central estimate of the adjustment factor for each of the categories (minor health effects, severe and chronic health effects, mortality, and visibility).

We previously examined how sensitive the estimate of total benefits is to alternative estimates of the income elasticities. Table 55 lists the ranges of elasticity values used to calculate the income adjustment factors, while Table 56 lists the ranges of corresponding adjustment factors. The results of this sensitivity analysis, giving the monetized benefit subtotals for the four benefit categories, are presented in Table 57.

Table 55. Ranges of Elasticity Values Used to Account for Projected Real Income Growth[a]

Benefit Category	Lower Sensitivity Bound	Upper Sensitivity Bound
Minor Health Effect	0.04	0.30
Mortality	0.08	1.00

[a]Derivation of these ranges can be found in Kleckner and Neumann, 1999. COI estimates are assigned an adjustment factor of 1.0.

Table 56. Ranges of Adjustment Factors Used to Account for Projected Real Income Growth[a]

Benefit Category	Lower Sensitivity Bound	Upper Sensitivity Bound
Minor Health Effect	1.018	1.147
Mortality	1.037	1.591

[a]Based on elasticity values reported in Table 55, U.S. Census population projections, and projections of real GDP per capita.

Table 57. Sensitivity of Monetized Benefits to Alternative Income Elasticities[a]

	Benefits Incremental to Baseline (Millions of 2006$)	
Benefit Category	Lower Sensitivity Bound	Upper Sensitivity Bound
Minor Health Effect	$30	$31
Mortality[b]	$3,600	$3,800

[a]All estimates rounded to two significant digits.

[b]Using mortality effect estimate from Krewski et al., 2000 and 3% discount rate. Results using Laden et al. (2006) or a 7% discount rate would show the same proportional range.

Consistent with the impact of mortality on total benefits, the adjustment factor for mortality has the largest impact on total benefits. The value of mortality in 2020 ranges from 96% to 108% of the main estimate based on the lower and upper sensitivity bounds on the income adjustment factor. The effect on the value of minor health effects is much less pronounced, ranging from 86% to 133% of the main estimate for minor effects.

6.4.4 Statistical Estimates of VSL

EPA relies on published peer-reviewed studies to provide statistical estimates of the value of avoided statistical mortality risk (VSL). These studies provide a range of differ estimates due to varying study design and different statistical samples. EPA uses a distribution of values fit to the studies' estimates as described in Section 5.1.1 and Table 22.

6.4.5 Alzheimer's Disease and Parkinson's Disease Onset Lifetime Costs

The epidemiologic study from with the risk estimates for Alzheimer's and Parkinson's disease were identified used time to first hospital admission as the health endpoint readout. As the authors note that this is not necessarily indicative of disease onset, we only include valuation estimates of associated

hospital admissions costs in the main benefits assessment. However, we include information here regarding how the benefits estimates would increase if the first hospital admission were used as a surrogate for disease onset.[87]

6.4.5.1 Alzheimer's Disease

Potential valuation sources of Alzheimer's disease lifetime medical costs were available from the Alzheimer's Association, 2020 report and Jutkowitz et al., 2017. Using Alzheimer's Association, 2020, we first developed an estimate of incremental annual medical expenses for Medicare beneficiaries living with Alzheimer's Disease (Table 58). Then, using the estimated life expectancy duration of 5 year from Jutkowitz et al., 2017, 3% and 7% discounted costs were extrapolated (Table 59). We note that the average/median age of Alzheimer's disease diagnosis/onset is after the age of 65, at which we assume retirement, so any potential lost wages are not included in this valuation estimate. Lifetime medical costs, excluding hospitalization, are estimated at $156,920 using a 3% discount rate or $145,946 using a 7% discount rate in 2015$ Alzheimer's Association, 2020.

Table 58. Annual Alzheimer's Disease Valuation Estimate Calculation

Service	**Beneficiaries with Alzheimer's Disease or Other Dementia**	**Beneficiaries without Alzheimer's Disease or Other Dementia**
Inpatient hospital	$11,465	$3,703
Medical provider	$5,762	$3,589
Skilled nursing facility	$7,213	$493
Nursing home	$16,523	$800
Hospice	$2,126	$161
Home health care	$2,661	$386
Prescription Medications	$3,481	$2,986
Annual Medical Expenses ($2019)	$49,231	$12,118
Annual Medical Expenses ($2015)	*$44,128*	*$10,862*
Incremental Annual Medical Expenses for Medicare beneficiaries with AD ($2015)	**$33,266**	

Table 59. Lifetime Alzheimer's Disease Valuation Estimate Calculation (2015$)

Year	**3% Discount Rate**	**7% Discount Rate**
0	$33,266	$33,266
1	$32,297	$31,090
2	$31,357	$29,056
3	$30,443	$27,155
4	$29,557	$25,379
Total Lifetime Costs	**$156,920**	**$145,946**

[87] Baseline incidence and prevalence data would need to be updated to estimate impacts of disease onset.

Jutkowitz et al., 2017 provided information needed to separately develop a lifetime Alzheimer's Disease cost estimate with a 3% discount rate, but not with a 7% discount rate (Table 60. Additional Lifetime Alzheimer's Disease Valuation Estimate Calculation with a 3% Discount Rate (2015$)). As the 3% discount rate estimate of $156,920 from Alzheimer's Association, 2020 is fairly similar to the lifetime 3% discount rate estimate of $184,500 from Jutkowitz et al., 2017, we have additional confidence in the validity of the Alzheimer's Association, 2020 estimates (Table 21).

Table 60. Additional Lifetime Alzheimer's Disease Valuation Estimate Calculation with a 3% Discount Rate (2015$)

Service	**Base-Case (83-year-old incident dementia case)**	**Counterfactual Dementia Free**	**Incremental Increase in Lifetime Costs**
Value of informal caregiving	$135,300	$2,460	$132,840
Out-of-pocket expenditures	$89,840	$64,720	$25,120
Medicaid expenditures	$44,090	$37,450	$6,640
Medicare expenditures	$52,540	$32,650	$19,890
Total value	$321,780	$137,280	**$184,500**

6.4.5.2 Parkinson's Disease

Yang et al., 2020 provided estimates of lifetime costs, including direct, indirect, and non-medical costs. Using Yang et al., 2020, we first developed an annual estimate of excess costs associated with living with Parkinson's Disease for one year (Table 61). Then, using the estimated life expectancy duration of 14.6 years from De Pablo-Fernandez et al., 2017, the 3% and 7% discounted costs were extrapolated (Table 62). Lifetime medical costs are estimated at $567,285 using a 3% discount rate or $445,792 using a 7% discount rate in 2015$ (Table 21).

Table 61. Annual Parkinson's Disease Valuation Estimate Calculation

Service	**Excess Cost per Person with Parkinson's Disease**	**Description**
Direct Medical Costs		
Non-acute institutional care	$6,888	Quantify excess healthcare cost of each person with Parkinson's Disease compared with 10 matched individuals without Parkinson's Disease
Hospital inpatient	$6,932	
Outpatient	$5,308	
Physician office	$1,182	
Durable medical equipment	$140	
Prescription medication	$3,988	
Direct Medical Costs Subtotal	*$24,438*	
Indirect Medical Costs		
Paid daily non-medical care	$3,709	Home caretakes/long-term care facilities
Home modification	$2,151	
Motor vehicle modification	$897	
Other expenses	$508	
Indirect Medical Costs Subtotal	*$7,265*	
Non-Medical Costs		
Reduced employment	$2,579	Reduced labor market participation due to early retirement
Absenteeism	$4,869	Lost work days
Presenteeism	$2,841	Lost work productivity at work
Social productivity loss in volunteer work	$997	
Supplemental security income (SSI)	$541	SS disability supplemental income
Social security disability insurance (SSDI)	$1,617	
Other disability income	$2,431	Includes other disability income sources such as VA disability, gov't employee disability, & state disability insurance or personal disability insurance payments
Non-Medical Costs Subtotal	*$18,293*	
Annual Medical Expenses ($2017)	$47,578	
Annual Medical Expenses ($2015)	**$44,718**	

Table 62. Lifetime Parkinson's Disease Valuation Estimate Calculation

Year	3% Discount Rate	7% Discount Rate
0	$44,718	$44,718
1	$43,416	$41,793
2	$42,151	$39,059
3	$40,924	$36,503
4	$39,732	$34,115
5	$38,574	$31,883
6	$37,451	$29,798
7	$36,360	$27,848
8	$35,301	$26,026
9	$34,273	$24,324
10	$33,275	$22,732
11	$32,305	$21,245
12	$31,364	$19,855
13	$30,451	$18,556
14	$29,564	$17,343
14.6	$17,427	$9,992
Total Lifetime Costs (14.6 yr survival)	*$567,285*	*$445,792*

6.5 Qualitative Characterization of Uncertainties

There are several uncertainties we are unable to fully or partially quantitatively assess, but qualitatively discuss below, in alphabetical order.

6.5.1 Applying Risk Estimates to Locations and Populations not Specified in the Epidemiologic Study

EPA regulatory actions often affect portions of the country and populations that differ from those considered in the epidemiologic studies providing the risk estimates. EPA commonly transfers risk estimates from one location or population to another, following a procedure called benefits transfer, a potential source of uncertainty. When available, risk estimates based on nationwide studies reflecting the overall population demographics of U.S. residents will be used when estimating health benefits. Epidemiologic studies exploring the relationship between air pollution and the risk of mortality often consider populations whose characteristics are broadly representative of the U.S. (e.g., Medicare-based estimates will be applied to those >64). By contrast, epidemiologic studies examining morbidity outcomes may focus on population subsets, such as those residing in specific geographic regions, a single sex, or selected races/ethnicities. In this context, two or more epidemiologic studies may report risk estimates that, when pooled, can better characterize risks experienced by U.S. populations. However, in some cases it may be scientifically inappropriate to pool risk estimates—for example, a nationwide analysis of populations ages 65-99 and a less-geographically diverse analysis of populations ages 0-99. In a situation such as this, the estimate best characterizing risk in the U.S. will be included in the main benefits assessment and the others will be included in quantitative sensitivity analyses (sections 6.1 and 6.1.6).

6.5.2 Causality Determination

When estimating air pollutant-attributable health impacts, EPA focuses on endpoints for which the underlying scientific evidence is strongest. This approach is based on evaluating evidence across scientific disciplines (i.e., clinical, animal toxicological, and epidemiologic) with regard to consistency of effects within a discipline, coherence of effects across disciplines, and evidence of biological plausibility. Such an approach gives us greater confidence in the relationship between exposure and health outcome. For criteria pollutants, EPA typically relies upon the causality determinations in the latest ISA or equivalent, which are made using a weight-of evidence approach. These causality determinations are, however, made for categories of health effects and not for specific endpoints. Thus, the extent to which the relationship exists for the specific endpoint and the exposure circumstances of interest in a benefits assessment is a source of uncertainty.

An expert elicitation sponsored by EPA to characterize the uncertainty in the relationship between $PM_{2.5}$ and mortality, including causal uncertainty, was released in 2006 and reviewed by the Advisory Council on Clean Air Compliance (Hammitt, 2008, IEc, 2006). Although the 12 expert-defined concentration-response functions provide useful information on the sensitivity of the health benefits estimates, additional epidemiology literature which addresses some of the weaknesses identified by the expert elicitation has since become available, such as improved exposure estimation techniques and the use of cohorts more representative of the U.S population. For these reasons we do not include the expert-derived results as a sensitivity analysis here but consider it as qualitative support for the relationship between long-term $PM_{2.5}$ exposures and all-cause mortality impacts.

Causal inference is another method of establishing a causal connection that evaluates associations under changing conditions. The 2019 PM ISA stated that "overall, the results of these causal inference studies contribute to the body of epidemiologic evidence that informs the causal relationship between long-term (one month to years) $PM_{2.5}$ exposure and total mortality (U.S. EPA, 2019c). Observing consistent results for this relationship across studies using different analytic techniques (i.e., difference-in-difference approach) increases our confidence in the relationship."

6.5.3 Estimating and Assigning Exposures in Epidemiology Studies

New developments in exposure assessment, including hybrid spatiotemporal models that incorporate satellite observations of aerial optical density, land use variables, surface monitoring data from monitors, and chemical transport models, have led to improvements in the spatial resolution extent of pollutant concentration surfaces. After reviewing the current state of exposure science, the 2019 PM ISA stated that "a number of studies demonstrate that the positive associations observed between long-term $PM_{2.5}$ exposure and mortality are robust to different methods of assigning exposure" and the 2020 O_3 ISA articulated that "hybrid methods have produced lower error predictions of ozone concentration compared with spatiotemporal models using land use and other geospatial data alone but may be subject to overfitting given the many different sources of data incorporated into the hybrid framework."

Although these advancements may reduce bias and uncertainty in risk estimates, the accuracy of hybrid exposure estimates is difficult to confirm in areas lacking monitors. On the other hand, studies using monitor data as the only exposure information have increasing exposure uncertainty the farther people live from the monitor site.

Uncertainties related to $PM_{2.5}$ and O_3 exposure estimation vary. For example, the $PM_{2.5}$ HBM method had Pearson *R*'s ranging from 0.91 to 0.94 when applied across the U.S. at a 36-km resolution, depending on the geoimputation approach of the CMAQ data (U.S. EPA, 2019c). The evaluation of the O_3 HBM method has been relatively limited. However, overall conclusions regarding long-term O_3 exposure estimates that include fixed-site monitor measurements are that "the true effect of long-term exposure to ambient ozone may be underestimated or overestimated by the model" and that it "is much more common for the effect estimate to be underestimated, and the bias is typically small in magnitude" (U.S. EPA, 2020a).

6.5.4 Differential Toxicity of $PM_{2.5}$ According to Chemical Composition

$PM_{2.5}$ is a heterogenous mixture of solid and liquid particles suspended in air and can vary with regards to size, composition, and source. The 2020 PM ISA found that "across exposure durations and health effects categories…many $PM_{2.5}$ components and sources are associated with many health effects, and the evidence does not indicate that any one source or component is consistently more strongly related to health effects than $PM_{2.5}$ mass;" although, it was also noted that "most studies that examine PM sources and components focused on $PM_{2.5}$" (U.S. EPA, 2019c).

Since the 2019 PM ISA concluded that "recent studies continue to demonstrate that no individual $PM_{2.5}$ component or source is a better predictor of mortality than $PM_{2.5}$ mass" and "many $PM_{2.5}$ components and sources are associated with many health effects and that the evidence does not indicate that any one source or component is consistently more strongly related with health effects than $PM_{2.5}$ mass" we continue to assume that all fine particles, regardless of their chemical composition, are equally potent in causing mortality and do not quantitatively assess uncertainties related to potential differences in $PM_{2.5}$ toxicity or composition. A qualitative discussion of this uncertainty as it relates to respiratory effects, cardiovascular effects, and mortality can be found in section 1.5.4 of the 2019 PM ISA (U.S. EPA, 2019c).

6.5.5 Different Long-Term Exposure Windows

The delay between changes in exposure and changes in health is an empirical challenge in estimating potential health effects associated with air pollution exposure. For example, if health impacts of high pollutant exposures have a long latency, risk estimates attributing to lower pollutant concentrations experienced more recently may be biased away from the null. However, the 2019 PM ISA states that "new evidence from recent studies continues to support the previous conclusion that health benefits from reducing air pollution could be expected with a few years of intervention" (U.S. EPA, 2019c). This issue is likely less relevant to O_3 exposure-attributable mortality, as those studies often have very similar, if not overlapping, health and air quality data.

6.5.6 Discounting Future Benefit Estimates

Discounting reflects that people prefer benefits presently more than in the future. When appropriately applied, discounting can allow for the direct comparison of future benefits to costs. However, there are potential uncertainties associated with discounting future benefit estimates. EPA bounds discounted benefits and costs using an estimate of the consumption rate of interest and a rate of return on private capital given that the share of capital that is displaced by a regulation is unknown. OMB currently recommends, and EPA uses, a real consumption rate of discount of 3% and a real rate of 7% for the opportunity cost of private capital based on prior empirical estimates (OMB, 2003). These values are

estimates and therefore introduce uncertainty. Additional detail on discounting can be found in the EPA *Guidelines for Preparing Economic Analyses* (U.S. EPA, 2014).

6.5.7 Statistical Estimates of WTP

EPA relies on published peer-reviewed studies to provide statistical estimates of the value of avoided pain and suffering (WTP). While most of these studies provide estimates of the uncertainty due to statistical sampling, there are other important sources of error. First, the statistical models used to produce these estimates may be incorrect, termed modeling error. Second, the statistical samples used to produce these estimates may be selectively chosen and unlike the population of interest, leading to selection error. Third, WTP values are unavailable for many health endpoints of interest. Assigning a value of zero is clearly incorrect, but the EPA has no basis on which to assign other values.

6.5.8 Confounding by Individual Risk Factors

Interindividual variability in both physiological responses and exposures to ambient air pollution can affect the size of reported risk estimates in epidemiologic studies. Well-designed epidemiology studies account for individual risk factors as covariates in their models[88], and so all else being equal we identify risk estimates adjusted to control for the most covariates that could reasonably impact the risk estimate. However, confounding by individual risk factors remains a potential source of uncertainty as additional relevant covariates may exist that are not included as covariates in epidemiological risk estimates used for health benefits assessment. Unfortunately, we are currently unable to quantitively assess this area of uncertainty but will include qualitative discussions when possible.

6.5.9 Confounding by Other Pollutants

When considering the relationship between pollutant exposure and health impacts, it can be informative to consider whether risk estimates are changed when other pollutants are included in copollutant models, especially when health impacts of multiple pollutants are being estimated concurrently. Regarding long-term exposures, the 2019 PM ISA concluded that "positive associations observed between long-term $PM_{2.5}$ exposure and total mortality remain relatively unchanged after adjustment for…NO_2 and $PM_{10–2.5}$" and the 2020 O_3 ISA found that "positive associations observed between long term O_3 exposure and total mortality remain relatively unchanged after adjustment for…NO_2." However, confounding due to the effects of copollutants other than O_3 and $PM_{2.5}$ are a potential source of uncertainty.

6.5.10 Risk Attributable to Long-Term and Short-Term Exposures

Long- and short-term exposures may follow similar or divergent biological pathways. When pathways are similar, estimates of impacts from long-term exposures may include short-term impacts and vice-versa. However, if pathways diverge, long- and short-term impacts may be the sum, or even greater than the sum, of the two exposure duration impacts. As there is little research directly comparing long- and short-term effects, we are currently unable to quantitatively assess this area of uncertainty for either $PM_{2.5}$- or O_3-attributable health effects.

[88] Common covariates include education level, marital status, body mass index, cigarette smoking, diet, occupational exposures, income, percentage of minority, unemployment, and poverty.

6.5.11 Heterogeneity of Risk Estimates

Epidemiologic studies often differ according to study design, geographic locations, age groups, population attributes, study size, methods for estimating exposure, range of pollutant concentrations, time periods, study sizes, and follow-up durations. These differences in turn influence the magnitude and standard error of study-reported risk estimates. The diversity of identified risk estimates could reflect either the variability across the populations studied or uncertainty around the risk estimates. Importantly, heterogeneous risk estimates are not necessarily indicative of bias, but could also result from variability of the underlying input parameters.

6.5.12 O_3 Metrics[89]

O_3 exposure metrics used to develop risk estimates can take many forms, though the most widely used metrics are the maximum daily 8-hour average (MDA8), daily average 24-hour (DA24), daily average 8-hr from 10AM to 6PM (DA8), and maximum daily 1-hour average (MDA1) metrics.

Historically, if epidemiologic studies developed risk estimates based on O_3 metrics other than MDA8, EPA would adapt the risk estimates based on average conversion ratios to be appropriate for use with air quality surfaces projected in the MDA8 metric (Anderson and Bell, 2010). This approach brings with it uncertainties associated with the simplifying assumptions used to develop the conversion ratios. In most cases, the day to day variation in different metrics (e.g., DA24 vs MDA8) is highly correlated. As such, the relationships between health impacts and different ozone metrics will also be highly correlated. However, when we apply risk estimates derived from time series results to evaluate the impacts of a specific policy scenario, we focus most on the shift in the overall distribution of O_3 concentrations over an entire season, instead of on the day to day variation in O_3 levels. Because specific policy scenarios might result in different temporal distributions of ozone concentrations than was observed in the monitored ozone data used in the studies, it is important to choose an O_3 metric that is best suited to capturing changes in O_3 that are likely to occur during hours where populations are likely to be exposed.

6.5.12.1 Converting O_3 Risk Estimate Exposure Metrics

When epidemiologic risk estimates are developed using non-MDA8 O_3 exposure metrics, EPA has typically converted the beta risk estimates into MDA8 metrics, which brings in a potential source of uncertainty (Anderson and Bell, 2010). We discuss uncertainties associated with converting various common O_3 exposure metrics into the MDA8 metric below.

6.5.12.1.1 DA24 to MDA8

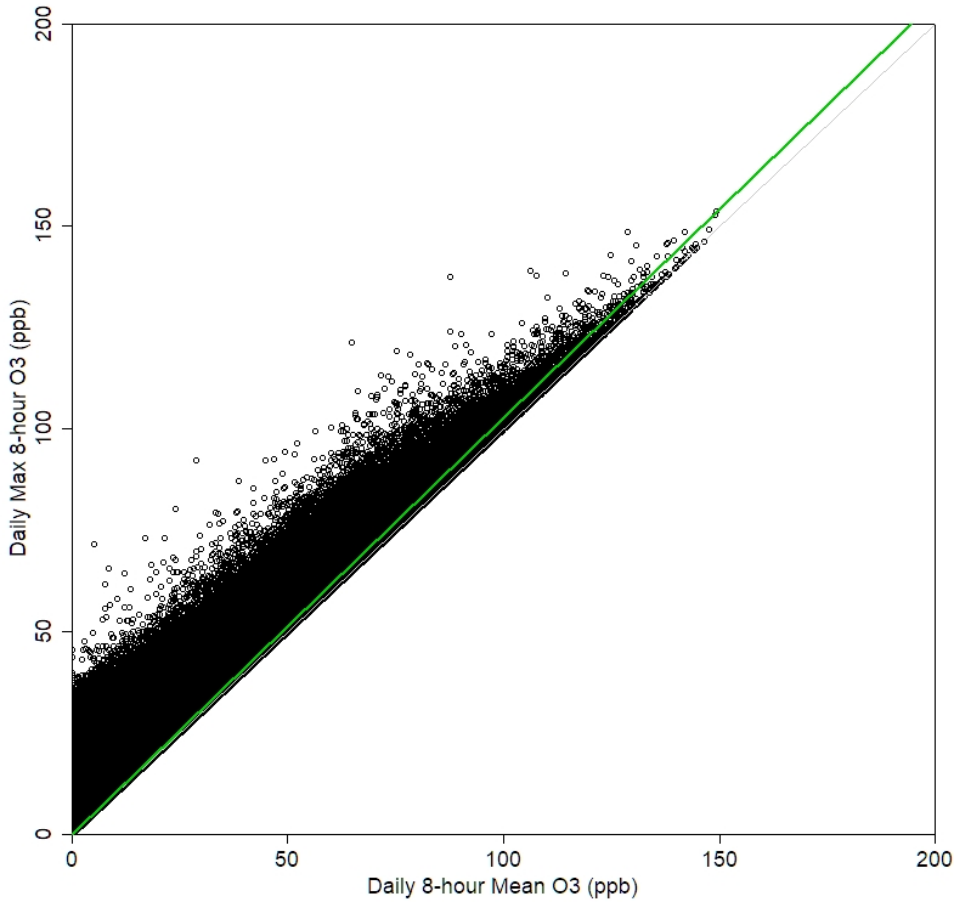
Currently, air quality projections using the MDA24 metric are unavailable, so a conversion factor from Anderson and Bell, 2010 is used in order to apply these risk estimates to MDA8 air quality surface projections. We multiply the beta risk estimate by the inverse of the median summer ratio of MDA8 to DA24 mean O_3 concentrations (i.e., 1 / 1.53 = 0.6536) for studies assessing summer O_3 exposure or by the inverse of the fixed effects average ratio of MDA8 to DA24 mean O_3 concentrations (i.e., 1 / 1.53 = 0.6536) for studies assessing all-year O_3 exposure. We note that Anderson and Bell, 2010 included a range of ratios from 1.23-1.83.

[89] $PM_{2.5}$ exposure metrics are not discussed here as the vast majority are based on daily 24-hour average concentrations and annual exposures are often estimated using daily 24-hour average concentrations. Importantly, this potential source of uncertainty is not likely to have a large effect on overall $PM_{2.5}$ benefits estimates results.

6.5.12.1.2 DA8 to MDA8

A comparison of the MDA8 and DA8 metrics using 20 years of O_3 monitoring data (2000-2019) for the entire contiguous U.S. resulted in a very high rate of correlation (Figure 17). The correlation was based on a simple linear regression with zero intercept, meaning that if the MDA8 is 0, then the DA8 mean must also be zero. The green line is the regression line and the light gray line represents a 1:1 relationship. Please note, the MDA8 cannot exceed the DA8 and the high density of the ~7 million points shown in the graph cluster near the 1:1 line. In fact, the MDA8 and DA8 metrics are identical approximately 30% of the time and differ by 2 ppb or less about 80% of the time. Based on this comparison, the conversion factor from DA8 to MDA8 is 0.97.

Figure 17. Correlation of MDA8 and DA8 O_3 Exposures Between 2000-2019 (R=0.986)



6.5.12.1.3 MDA1 to MDA8

Due to time and resource limitations, air quality projections using the MDA1 metric are also unavailable for the Revised CSAPR Update final rulemaking, so a conversion factor from Anderson and Bell, 2010 is used in order to apply these risk estimates to MDA8 air quality surface projections. We multiply the beta risk estimate by the median summer ratio of MDA1 to MDA8 O_3 concentrations (i.e., 1.13) for studies assessing summer O_3 exposure or by the fixed effects average ratio of MDA1 to MDA8 O_3 concentrations (i.e., 1.14) for studies assessing all-year O_3 exposure. We note that Anderson and Bell, 2010 included a range of ratios from 1.08-1.26.

6.5.13 O_3 Season

Studies of O_3 vary with regards to O_3 season, limiting analyses to various definitions of summer (e.g., April-September, May-September or June-August) and exposures over the full calendar year. These differences can reflect state-specific, EPA-defined O_3 seasons or another seasonal definition chosen by the study author. O_3 exposure estimates are arguably more accurate during the summer when concentrations are typically higher and more monitors are operational. In addition, respiratory effects associated with short-term exposures are commonly limited to the warm season and therefore reflect the incidence that occurs during the 5- or 6-month O_3 season (U.S. EPA, 2020d). Recently, there are an increased number of long-term analyses of O_3-attributable health impacts over the full calendar year using hybrid modeling techniques and where O_3 monitoring data is collected for the entire year. These studies likely represent a more complete estimate of O_3-attributable health impacts.

While epidemiologic studies assessing all-year O_3 exposures would likely present more comprehensive estimates of health impacts, hybrid O_3 surface projections for baseline and policy rulemaking scenarios are not currently available.[90] As such, we identified epidemiologic studies and associated risk estimates that evaluated associations between exposures and warm season effects when available. There was some variability amongst the warm season definitions within the list of studies identified in this update (e.g., April-September and June-August), although only the respiratory emergency department and asthma symptom risk estimate was based on full year O_3 exposures (Barry et al., 2019, Lewis et al., 2013). It should be noted that the exposures for asthma symptoms among the identified studies were not evenly distributed across all the seasons (I.e. three in Spring, two in Summer, two in Fall, and one in Winter).[91]

There is some variability regarding the definition of the warm season amongst epidemiologic studies included in the ISAs and the main risk estimates identified here for O_3 benefits estimates. When there is a substantial difference, such as the June-August warm season assessed by Zanobetti and Schwartz, 2008, we develop season-specific air quality projections, when feasible. However, many studies begin the 5-7 month warm season in either April or May and conclude the season in September or October. Since projected full year hybrid O_3 surfaces are currently not available, epidemiologic risk estimates will be applied to the air quality projection most closely matching the exposure season in the study (e.g., April-September exposures will be applied to May-September air quality projections). We expect this seasonal mismatch will only have a limited effect on the magnitude of related health incidence.

6.5.14 Shape of the Concentration-Response Relationship

6.5.14.1 $PM_{2.5}$

An important consideration when characterizing uncertainty is whether the concentration-response relationship is linear across the full concentration range that is encountered, or if there are concentration ranges where there are departures from linearity. Overall, evidence from the 2019 PM

[90] The paucity of O_3 monitoring data in winter months potentially complicates the development of full year projected O_3 surfaces, which would need to be subject to comprehensive evaluation prior to use in EPA RIAs.

[91] When risk estimates based on full-year, long-term O_3 exposures are applied to warm season air quality projections, the resulting benefits assessment may underestimate impacts, due to a shorter timespan for impacts to accrue. When risk estimates based on full-year, short-term O_3 exposures are applied to warm season air quality projections, the resulting benefits assessment may also underestimate impacts, as short-term O_3 exposure effects are typically larger during the warm season (U.S. EPA, 2020a).

ISA continues to "support a linear, no-threshold concentration-response relationship for long-term exposure to $PM_{2.5}$ and total (nonaccidental) mortality, especially at lower ambient $PM_{2.5}$ concentrations, with confidence in some studies in the range of 5−8 μg/m^3" and "there is less certainty in the shape of the concentration-response curve at mean annual $PM_{2.5}$ concentrations generally below 8 μg/m^3, although some studies characterize the concentration-response relationship with certainty down to 4 μg/m^3" (U.S. EPA, 2019c).

Although ten large cohort studies of long-term $PM_{2.5}$-attributable mortality observed linear, no-threshold concentration-response relationships, three Canadian studies presented evidence of deviations from linearity down to the lowest concentration evaluated. Two studies found evidence of a supralinear relationship at lower concentrations, although only one was statistically significant. And a single study found that the best fit for the long-term $PM_{2.5}$ mortality relationship was in a threshold model with a threshold at 11 μg/m^3.

There are several potential explanations for these results, one of which is that studies may be unable to adequately evaluate the relationship at low levels without sufficient population exposure at those levels. Consistent with that hypothesis, the single statistically significant study finding evidence of supralinearity did have one of the lowest mean $PM_{2.5}$ concentrations, at 6.3 μg/m^3. Another possible explanation with support from the 2019 ISA is that the shape of the concentration-response relationship could differ by health outcome.

Although there were no evaluations of the shape of the long-term $PM_{2.5}$-attributable respiratory mortality relationship in the 2019 PM ISA, there were several studies of the relationship between long-term $PM_{2.5}$exposure and cardiovascular disease. When considering long-term $PM_{2.5}$-attributable cardiovascular mortality, again most results "continue to support a linear, no-threshold relationship…especially at lower ambient concentrations of $PM_{2.5}$…[with] a number of the concentration-response analyses include concentration ranges ≤12 μg/m^3." As with total mortality, a few studies found that risk was greater at lower concentrations, although the deviation from linearity was not statistically significant. The only evidence of nonlinearity in the long-term $PM_{2.5}$-attributable cardiovascular mortality relationship came from two studies by the same group, which included exposure from cigarette smoking. They observed that the concentration-response relationship was much steeper at lower $PM_{2.5}$ concentrations, such as those due to ambient air pollution, than at the higher concentrations associated with cigarette smoking.

There were a small number of studies of the relationship between long-term $PM_{2.5}$ exposure and cardiovascular morbidity endpoints in the 2019 PM ISA. A study of hypertension and another of ischemic heart disease incidence found no deviations from linearity. Two studies of coronary artery calcification found evidence of deviations from linearity, but the direction of the results was inconsistent. One study found evidence of sublinearity at higher concentrations while the other found evidence of supralinearity at both high and low concentrations.

The shape of the relationships between $PM_{2.5}$ exposure and health effects may also include a threshold, or $PM_{2.5}$ exposure concentration below which human health is not adversely impacted. Although evidence does not currently support the existence of a measurable $PM_{2.5}$ exposure population-level threshold, prior higher concentration exposures with longer latency periods could make thresholds difficult to detect. However, the 2019 PM ISA states that "new evidence from recent studies continues

to support the previous conclusion that health benefits from reducing air pollution could be expected with a few years of intervention," reducing the likelihood of this potential source of uncertainty.

Based on the evidence and lack of nonlinear relationships between long-term $PM_{2.5}$ exposure and health impacts, we continue to assume a linear, no-threshold relationship and do not quantitatively assess uncertainties related to the shape of the concentration-response relationships

6.5.14.2 O_3

The 2020 final O_3 ISA evaluated a number of studies examining the shape of the concentration-response relationship for long term O_3 exposure and mortality using various different statistical techniques, including linear models and restricted cubic splines, which we use to inform the long-term O_3-attributable respiratory mortality relationship (U.S. EPA, 2020a). The ISA concluded that:

> *Generally linear, no-threshold relationships exist down to 35–40 ppb, although the results were not entirely consistent. Some studies observed a sublinear relationship, indicating larger changes in risk for higher O_3 concentrations compared with lower O_3 concentrations. Several studies also included threshold analyses and support the possibility of a threshold near 35 to 40 ppb*. (U.S. EPA, 2020a, section 6.2.7)

The ozone ISA also found that:

> *Recent multicity studies continue to support a linear [concentration-response] relationship with no evidence of a threshold between short term ozone exposure and mortality over the range of ozone concentrations typically observed in the U.S. Studies that used different statistical approaches and ozone averaging times (i.e., 24 hour avg and 8 hour max) provide evidence of a linear concentration-response relationship, with less certainty in the shape of the curve at lower concentrations [i.e., 40 ppb for 24 hour avg and 30 ppb for 8 hour max]. An examination of whether a threshold exists in the ozone mortality concentration-response relationship provided no evidence of a concentration below which mortality effects do not occur when examining 5 $\mu g/m^3$ (~2.55 ppb) increments across the range of 1 hour max concentrations reported in the U.S. and Canadian cities included in [a large cohort].* (U.S. EPA, 2020a, section 6.1.8)

Collectively, these results continue to support the conclusion of the 2006 Ozone Air Quality Criteria Document that "if a population threshold level exists in ozone health effects, it is likely near the lower limit of ambient ozone concentrations in the U.S." and this we assume linear, no-threshold relationships exist between ozone and health impacts in the main benefits estimate.

In addition, the studies identified as best characterizing respiratory mortality exposures did not provide threshold models or find evidence supporting a threshold associated with warm-season effects. Turner et al., 2016 did find "some evidence that a threshold model improved model fit for respiratory mortality at 35 ppb (P = 0.002) compared with a linear model using year-round but not summertime O_3 (HR per 10 ppb using threshold O_3 indicator at 35 ppb for respiratory mortality, 1.17; 95% CI, 1.11–1.22)." However, as we are currently unable to obtain all year air quality projections, we are unable to quantitatively assess this year-round-specific uncertainty associated with long-term O_3 exposures.

6.5.15 Short-Term Lag Structure[92]

Epidemiologic analyses of short-term exposures often present results as health outcomes occurring a certain time period, or lag days, after exposure. Although there are means of aggregating outcomes that do not occur simultaneously, such as distributed or multi-day lags, there is a possibility that the full impact may not be captured by discrete lag periods in short-term study results. Although uncertainty remains as to whether short-term health impacts are fully captured by discrete lag durations, potentially biasing results toward the null, we are currently unable perform quantitative uncertainty analyses regarding this source of uncertainty.

6.5.15.1 $PM_{2.5}$

The 2019 final PM ISA states that "a number of recent studies conducted systematic evaluations of the lag structure of associations for the [short-term] $PM_{2.5}$ [exposure]-mortality relationship by examining either multiday lags or a series of single-day lags, and these studies continue to support an immediate effect (i.e., lag 0-1 days) of short-term $PM_{2.5}$ exposures on mortality." With respect to morbidity effects, the ISA found that "while recent studies provided evidence of associations in the range of 0-5 days for respiratory effects, there was evidence of an immediate effect for cardiovascular effects and mortality (i.e., 0-1 days) with some initial evidence of associations occurring over longer exposure durations (e.g., 0-4 days)."

6.5.15.2 O_3

The 2020 final O_3 ISA found that "for respiratory health effects, when examining more overt effects, such as respiratory related hospital admissions and ED visits (i.e., asthma, COPD, and all respiratory outcomes), epidemiologic studies reported strongest associations occurring within the 1st few days of exposure (i.e., in the range of 0 to 3 days)."

6.5.16 Statistical Technique/Model Used to Quantify Risks in Epidemiologic Study

Multiple statistical techniques are used in epidemiological analyses, including the Cox proportional hazards model and the Poisson survival analysis.

6.5.16.1 $PM_{2.5}$

The 2019 PM ISA compared the use of various statistical techniques, spatial random effects, and fixed[93] effect models (U.S. EPA, 2019c). The ISA found that "results from well-studied, highly regarded cohorts help to reduce uncertainties that the observed associations between long-term $PM_{2.5}$ exposure and mortality could be due to the statistical techniques employed or model specification."

6.5.16.2 O_3

The 2020 O_3 ISA found that "studies used a number of different statistical techniques to evaluate the shape of the [long-term exposure] concentration-response function, including linear models and restricted cubic splines, and generally observed linear, no-threshold relationships down to 35−40 ppb, although the results are not entirely consistent" (U.S. EPA, 2020a).

[92] The 2019 PM ISAs includes Table A-1 in its appendix, which describes the lag hierarchy preferences followed when identifying risk estimates for benefits assessment.

[93] Assumes that there is a single true concentration-response relationship and therefore a single true value for the risk estimate parameter that applies everywhere.

6.5.17 Temperature and Weather

Temperature and weather may impact observed associations between air pollution exposure and health effects in epidemiologic studies, especially in short-term exposure studies. Although a few studies attempt to disentangle the influence of temperature and/or weather, there is insufficient information available to perform quantitative assessments of uncertainty.

6.5.17.1 $PM_{2.5}$

The PM ISA included a number of studies that assessed whether statistical models adequately account for temporal trends and weather covariates. The ISA found that:

> Across studies that evaluated model specification, [short-term] $PM_{2.5}$-mortality, associations remained positive, although in some cases were attenuated, when using different approaches to account for temporal trends or weather covariates. Seasonal analyses continue to provide evidence that associations are larger in magnitude during warmer months, but it remains unclear whether copollutants confound the associations observed. In addition to seasonal analyses, some studies also examined whether temperature modifies the [short-term] $PM_{2.5}$-mortality relationship. Initial evidence indicates that the $PM_{2.5}$-mortality association may be larger in magnitude at lower and higher temperatures, but this observation has not been substantiated by studies conducted in the U.S. (U.S. EPA, 2019c, section 11.1.12)

6.5.17.2 O_3

Temperature and weather can also impact epidemiologic results, especially in short-term exposure analyses. While there is limited evidence of differential O_3 mortality associations by season, the 2020 O_3 ISA determined that the most extensive analyses conducted by recent studies examined whether temperature (i.e., long-term average temperatures or the distribution of mean daily temperatures) modifies the O_3 mortality association. Analyses focusing on temperature indicate that locations with lower long-term average temperature have higher O_3 mortality risk estimates, which is also reflected by the observed difference in risk estimates between northern and southern U.S. cities in a single study. However, as long term average temperature may be a surrogate for air conditioning prevalence and studies that examined either the joint or stratified effects of O_3 and temperature on mortality provided evidence of O_3 mortality associations that are larger in magnitude at temperature extremes, we do not plan on including quantitative uncertainty analyses for the effect of temperature on ozone effects.

6.5.18 Unquantified Impacts

As with all estimates of benefits, due to the lack of complete data, not all human health impacts attributable $PM_{2.5}$ and O_3 can be identified and quantified. EPA acknowledges the existence of unquantified impacts, such as subclinical health endpoints (e.g., hypertension, inflammation, changes in lung/heart function, etc.) or pollutant-attributable clinical endpoints not evaluated in epidemiologic studies.

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