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U.S. Environmental Protection Agency Clean Air Scientific Advisory Committee (CASAC)
Public Meeting

Review of the Integrated Science Assessment for Particulate Matter
External Review Draft

National Center for Environmental Assessment
Office of Research and Development
Washington, DC, December 12-13, 2018

EPA Speakers

- ORD/NCEA
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  - Jason Sacks, Staff lead on the ISA (EMAG)
- OAR/OAQPS/HEID
  - Erika Sasser, Director
- Additional EPA staff
  - Karen Wesson, Group Leader (HEID/ASG)
  - Robert Wayland, Group Leader (HEID/RBG)
  - Scott Jenkins, Staff lead on PM NAAQS (HEID/ASG)
  - Zachary Pekar (HEID/RBG)
  - Sheila Igoe and David Orlin (OGC)

Office of Air and Radiation (OAR)
- Office of Air Quality Planning and Standards (OAQPS)
  - Health and Environmental Impacts Division (HEID)
    - Ambient Standards Group (ASG)
    - Risk and Benefits Group (RBG)
  - Air Quality Assessment Division (AQAD)

Office of Research and Development (ORD)
- National Center for Environmental Assessment (NCEA)
  - Environmental Media Assessment Group (EMAG)

Office of General Counsel (OGC)

Outline for Presentation

- Introduction and Background
  - Statutory requirements
  - Current PM NAAQS
  - Initiation of expedited review
  - Timeline and role of CASAC in the current review
- Overview of the Draft ISA
  - Process for evaluating the scientific evidence
  - Scope of the ISA
  - Conclusions

Introduction and Statutory Requirements

- EPA sets national ambient air quality standards (NAAQS) for six pollutants
  - Ground-level ozone
  - Carbon monoxide
  - Nitrogen dioxide
  - Particulate matter
  - Lead
  - Sulfur dioxide

- Sections 108 and 109 of the Clean Air Act govern the establishment, review, and revision (as appropriate) of NAAQS, including:
  - **Primary (health-based) standards** which in the “judgment of the Administrator” are “requisite to protect the public health”, including at-risk populations, with an “adequate margin of safety”
  - **Secondary (welfare-based) standards** which in the “judgment of the Administrator” are “requisite to protect the public welfare from any known or anticipated adverse effects”

- The law requires EPA to review the scientific information and NAAQS for each criteria pollutant every five years, and to obtain advice from the Clean Air Scientific Advisory Committee (CASAC) on each review.

- Court decisions provide additional guidance on aspects of EPA decision-making
  - EPA is required to engage in “reasoned decision making” to translate scientific evidence into standards
  - EPA may not consider cost in setting standards; however, cost is considered in developing control strategies to meet the standards (implementation phase)

Statutory Requirements: CASAC

- Section 109(d)(2) addresses the appointment and advisory functions of an independent scientific review committee
- Section 109(d)(2)(B) provides that, at 5-year intervals, this committee "shall complete a review of the criteria…and the national primary and secondary ambient air quality standards…and shall recommend to the Administrator any new…standards and revisions of existing criteria and standards as may be appropriate…".
- Section 109(d)(2)(C) reads: "Such committee shall also
  - (i) advise the Administrator of areas in which additional knowledge is required to appraise the adequacy and basis of existing, new, or revised national ambient air quality standards,
  - (ii) describe the research efforts necessary to provide the required information,
  - (iii) advise the Administrator on the relative contribution to air pollution concentrations of natural as well as anthropogenic activity, and
  - (iv) advise the Administrator of any adverse public health, welfare, social, economic, or energy effects which may result from various strategies for attainment and maintenance of such national ambient air quality standards.

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Overview of Current PM NAAQS

Current Standards – Last Review Completed in 2012*					Decisions in 2012 Review
Indicator	**Averaging Time**	**Primary/Secondary**	**Level**	**Form**	
PM$_{2.5}$	Annual	Primary	12.0 $\mu g/m^3$	Annual arithmetic mean, averaged over 3 years	Revised level from 15 to 12 $\mu g/m^{3**}$
		Secondary	15.0 $\mu g/m^3$		Retained**
	24-hour	Primary and Secondary	35 $\mu g/m^3$	98th percentile, averaged over 3 years	Retained
PM$_{10}$	24-hour	Primary and Secondary	150 $\mu g/m^3$	Not to be exceeded more than once per year on average over a 3-year period	Retained

*Prior to 2012, PM NAAQS were reviewed and revised several times – established in 1971 (total suspended particulate – TSP) and revised in 1987 (set PM$_{10}$), 1997 (set PM$_{2.5}$), 2006 (revised PM$_{2.5}$, PM$_{10}$)

**EPA eliminated spatial averaging for the annual standards

Initiation of Expedited Review (May 2018 memo)

May 9, 2018 memo from the EPA Administrator:

- Directed the initiation of an expedited review of the PM NAAQS, targeting completion by the end of 2020
  - Also specified expedited review of NAAQS for ozone
- Identified ways to streamline the review process (e.g., increased focus on policy-relevant information and avoiding multiple drafts of documents)
- Identified standardized set of charge questions for CASAC including:
  - General charge questions for NAAQS reviews, to be supplemented with more detailed requests as necessary
  - Two additional charge questions that may elicit information not relevant to the standard-setting process.
    - EPA may consider an appropriate mechanism, including after receiving CASAC's final advice on the standards, to facilitate robust feedback on these topics

Timeline and CASAC Role in the Current Review

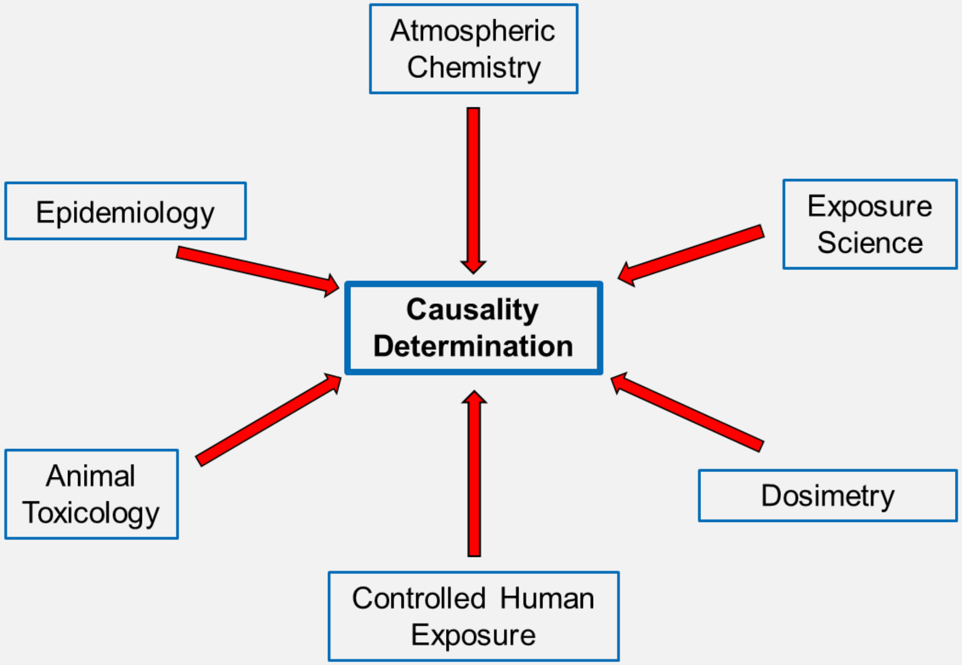
Date	EPA	CASAC
Dec 2014	Call for Information	
Feb 2015	Kickoff Workshop	
April 2016	Draft IRP	**Reviewed** the draft IRP, which presented the plan for reviewing the air quality criteria and the NAAQS for PM
Dec 2016	Final IRP	
Oct-Dec 2018	**Draft ISA**	**Review** draft ISA, which provides an assessment of the currently available scientific information on public health and welfare effects of PM and is the science foundation for the review *(the air quality criteria)*
Summer 2019	**Draft PA** (with REA analyses)	**Review** draft PA, which presents an evaluation of the policy-relevant aspects of the current scientific evidence and quantitative risk and air quality analyses, focusing on implications with regard to the adequacy of the current standards and, as appropriate, potential alternatives
2019-2020	**Final ISA** **Final PA**	
Spring 2020	**Proposed decision**	
Dec 2020	**Final decision**	

Weight-of-Evidence Approach for Causality Determinations for Health and Welfare Effects

- Provides transparency through structured framework
- Developed and applied in ISAs for all criteria pollutants
- Emphasizes synthesis of evidence across scientific disciplines (e.g., controlled human exposure, epidemiologic, and toxicological studies)
- Five categories based on overall weight-of-evidence:
  - Causal relationship
  - Likely to be a causal relationship
  - Suggestive of, but not sufficient to infer, a causal relationship
  - Inadequate to infer the presence or absence of a causal relationship
  - Not likely to be a causal relationship
- ISA Preamble describes this framework
  - Preamble is now stand-alone document (http://www.epa.gov/isa)
- CASAC reviewed the Agency's causal framework **~13 times** by **~90** CASAC charter and ad hoc panel members in the process of reviewing ISAs from 2008 – 2015; its use was supported in all ISAs

Evaluation of the Scientific Evidence

- Organize relevant literature for broad health outcome categories
- Evaluate studies, characterize results, extract relevant data
- Integrate evidence across disciplines for health outcome categories
- Develop causality determinations using established framework
- Evaluate evidence for populations potentially at increased risk
- Consideration of evidence spans many scientific disciplines from source to effect:
  - Atmospheric chemistry
  - Exposure
  - Controlled human exposure studies
  - Epidemiologic studies
  - Animal toxicologic studies
  - At-risk populations/lifestages


Atmospheric Chemistry
Epidemiology
Exposure Science
Causality Determination
Animal Toxicology
Dosimetry
Controlled Human Exposure

****Informs Hazard Identification step of Risk Assessment Process****

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Framework for Causality Determinations in the ISA

	Health Effects	**Ecological and Other Welfare Effects**
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 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.	Evidence is sufficient to conclude that there is a causal relationship with relevant pollutant exposures. That is, the pollutant has been shown to result in effects in studies in which chance, confounding, and other biases could be ruled out with reasonable confidence. Controlled exposure studies (laboratory or small- to medium-scale field studies) provide the strongest evidence for causality, but the scope of inference may be limited. Generally, the determination is based on multiple studies conducted by multiple research groups, and evidence that is considered sufficient to infer a causal relationship is usually obtained from the joint consideration of many lines of evidence that reinforce each other.
Likely to be a causal relationship	Evidence is sufficient to conclude that a causal relationship is likely to exist with relevant pollutant exposures. 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.	Evidence is sufficient to conclude that there is a likely causal association with relevant pollutant exposures. That is, an association has been observed between the pollutant and the outcome in studies in which chance, confounding, and other biases are minimized but uncertainties remain. For example, field studies show a relationship, but suspected interacting factors cannot be controlled, and other lines of evidence are limited or inconsistent. Generally, the determination is based on multiple studies by multiple research groups.
Suggestive of, but not sufficient to infer, a causal relationship	Evidence is suggestive of a causal relationship with relevant pollutant exposures but is limited, and chance, confounding, and other biases cannot be ruled out. For example: (1) when the body of evidence is relatively small, at least one high-quality epidemiologic study shows an association with a given health outcome and/or at least one high-quality toxicological study shows effects relevant to humans in animal species, or (2) when the body of evidence is relatively large, evidence from studies of varying quality is generally supportive but not entirely consistent, and there may be coherence across lines of evidence (e.g., animal studies or mode of action information) to support the determination.	Evidence is suggestive of a causal relationship with relevant pollutant exposures, but chance, confounding, and other biases cannot be ruled out. For example, at least one high-quality study shows an effect, but the results of other studies are inconsistent.
Inadequate to infer a causal relationship	Evidence is inadequate to determine that a causal relationship exists with relevant pollutant exposures. The available studies are of insufficient quantity, quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an effect.	Evidence is inadequate to determine that a causal relationship exists with relevant pollutant exposures. The available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an effect.
Not likely to be a causal relationship	Evidence indicates there is no causal relationship with relevant pollutant exposures. Several adequate studies, covering the full range of levels of exposure that human beings are known to encounter and considering at-risk populations and lifestages, are mutually consistent in not showing an effect at any level of exposure.	Evidence indicates there is no causal relationship with relevant pollutant exposures. Several adequate studies examining relationships with relevant exposures are consistent in failing to show an effect at any level of exposure.

Multiple, high-quality studies
Rule out chance, confounding, and other biases with reasonable confidence

Multiple, high-quality studies
Important uncertainties remain

Evidence is suggestive but limited

Evidence is of insufficient quantity, quality, consistency, or statistical power

Multiple studies show no effect across exposure concentrations

Contents of the Draft PM ISA

Preface: Legislative Requirements of the PM NAAQS, Purpose and Overview of the ISA, Process for Developing ISA

Executive Summary

Chapter 1. Integrated Synthesis

Chapter 2. Sources, Atmospheric Chemistry, and Ambient Concentrations

Chapter 3. Exposure to Ambient PM

Chapter 4. Dosimetry of PM

Chapters 5 - 11. Respiratory Effects, Cardiovascular Effects, Metabolic Effects, Nervous System Effects, Reproductive and Developmental Effects, Cancer, and Mortality

Chapter 12. Lifestages and Populations Potentially at Increased Risk of a PM-related Health Effect

Chapter 13. Welfare Effects

Scope of PM ISA

- **Scope:** The ISA is tasked with answering the question "Is there an independent effect of PM on health and welfare at relevant ambient concentrations?"
  - Health Effects
    - ○ Studies will be considered if they include a composite measure of PM (e.g., $PM_{2.5}$ mass, $PM_{10\text{-}2.5}$ mass, ultrafine particle (UFP) number)
      - ○ Studies of source-based exposures that contain PM (e.g., diesel exhaust, wood smoke, etc.) if they have a composite measure of PM and examine effects with and without particle trap to assess the particle effect
      - ○ Studies of components of PM if they include a composite measure of PM to relate toxicity of component(s) to current indicator
    - ○ Studies will be considered if PM exposures are relevant to ambient concentrations (< 2 mg/m^3; 1 to 2 orders of magnitude above ambient concentrations)

Previously reviewed by CASAC and detailed in the Integrated Review Plan

Scope of PM ISA (cont.)

- Welfare Effects
  - Focus is on non-ecological welfare effects
    - Visibility Impairment
    - Climate Effects
    - Materials Effects
  - Ecological effects resulting from the deposition of PM and PM components are being considered as part of the review of the secondary (welfare-based) NAAQS for oxides of nitrogen, oxides of sulfur and PM

Previously reviewed by CASAC and detailed in the Integrated Review Plan

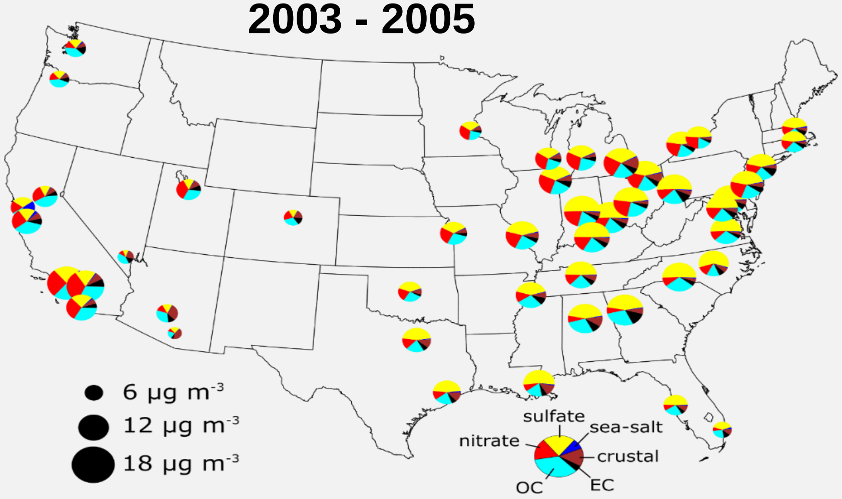
Executive Summary and Chapter 1

- Executive Summary
  - High-level overview of main conclusions of the entire ISA
  - Briefly captures strengths, limitations, and remaining uncertainties in the evidence base
- Integrated Synthesis (Chapter 1)
  - More detailed synthesis of the scientific evidence compared to the Executive Summary
    - Focus is on those health and welfare effects where it was concluded that a *causal* or *likely to be causal* relationship exists
    - Broad characterization of uncertainties and limitations in the evidence for $PM_{10\text{-}2.5}$ and UFPs that contributed to a *suggestive of, but not sufficient to infer* and *inadequate* causality determination
  - Integrated discussion of policy-relevant issues (e.g., copollutant confounding, concentration-response relationship, sources and components, etc.) spanning the health effects evidence
  - More detailed characterization of the strengths, limitations, and remaining uncertainties in the evidence base

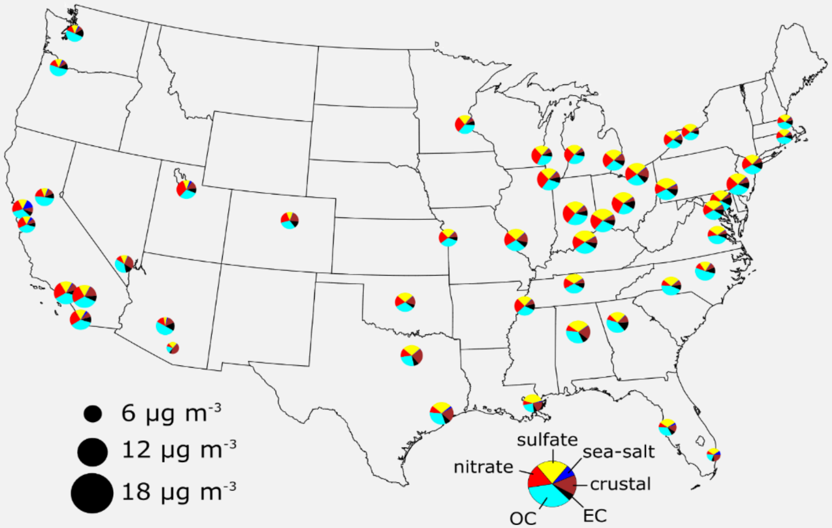
PM Concentrations and Trends (Chapter 2)

- $PM_{2.5}$
  - Steady declining trend 2000 to 2015, with most of the U.S. with annual average < 12 $\mu g/m^3$
  - Annual average decreased from 12 $\mu g/m^3$ to 8.6 $\mu g/m^3$ from 2006 to 2014
- $PM_{10-2.5}$
  - Federal Reference Method (FRM) in 2011
  - Recent data indicates that the contribution of $PM_{10-2.5}$ to PM_{10} is higher than previously reported
- UFPs
  - Highly variable concentration in space and over time due to physical and chemical processing in the atmosphere
  - UFP measured using multiple methods, varying in the size ranges examined
  - No U.S. monitoring network
- $PM_{2.5}$ Components
  - Organic carbon has replaced sulfate as the most abundant component of $PM_{2.5}$ in many locations, specifically in the eastern U.S.

2003 - 2005


6 µg m-3
12 µg m-3
18 µg m-3
sulfate
sea-salt
nitrate
crustal
OC
EC

2013 - 2015


6 µg m-3
12 µg m-3
18 µg m-3
sulfate
sea-salt
nitrate
crustal
OC
EC

Exposure to PM (Chapter 3)

- **Potential Errors and Uncertainty**
  - Vary depending on the exposure assessment method used
  - Evaluations more often occur for methods used in long-term exposure studies
- **Exposure Error**
  - **Short-term exposure studies:** exposure error produces underestimation of health effects
  - **Long-term exposure studies:** exposure error produces underestimation or overestimation of health effects
    - Overestimation of health effects occurs if the exposure model has low spatial resolution and underestimates exposures
- **Overall**
  - Necessary to examine individual study details to evaluate potential errors and uncertainty as well as quality of the exposure assessment method used

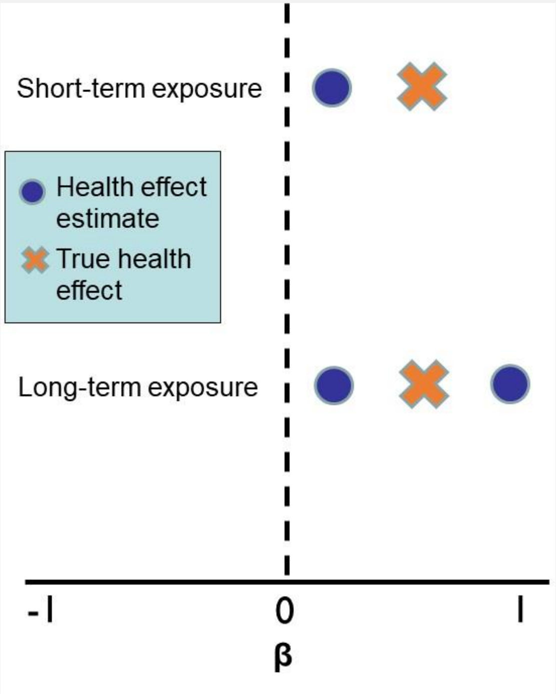
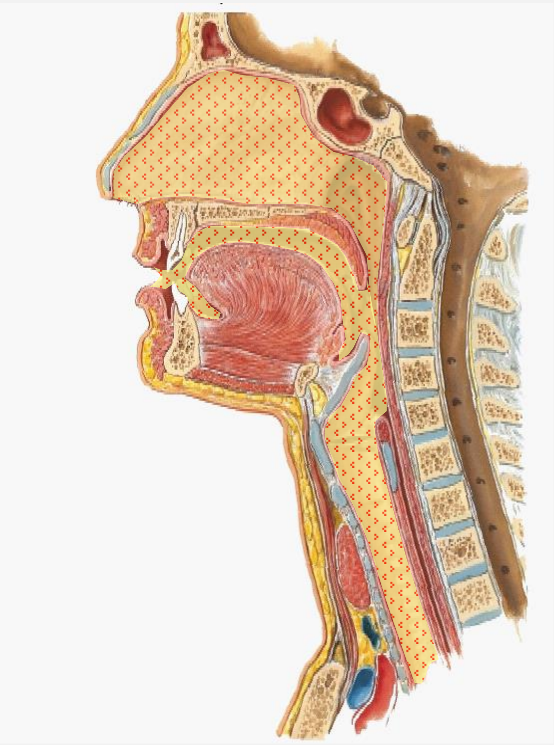

Short-term exposure
● Health effect estimate
✖ True health effect
Long-term exposure
-1
0
1
β

Figure. Influence of exposure error on health effects associations.

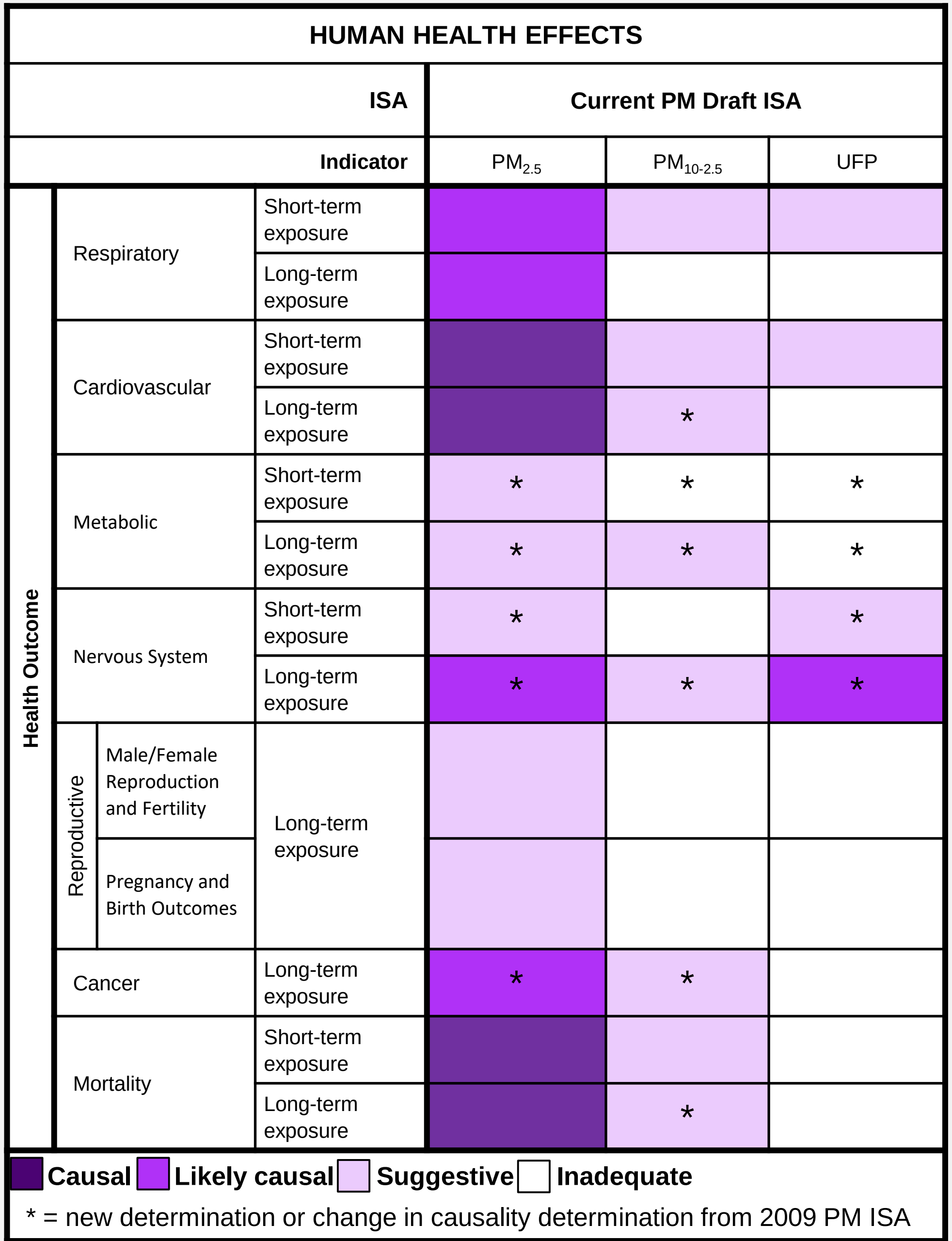
Dosimetry of PM (Chapter 4)

- New information in this review:
  - Demonstrates that children inhale less through the nose and have lower nasal deposition efficiency than adults resulting in increased exposure of the lungs to inhaled PM
  - Shows the translocation of a small fraction of particles (≤ 0.2 μm) out of the respiratory tract from the:
    - Olfactory mucosa to the brain
    - Alveolar region of the lung into blood
  - Indicates that PM_{10} overestimates the size of particles likely to enter the human lung



Oronasal breathing

Draft PM ISA
Health Effects: Causality Determinations



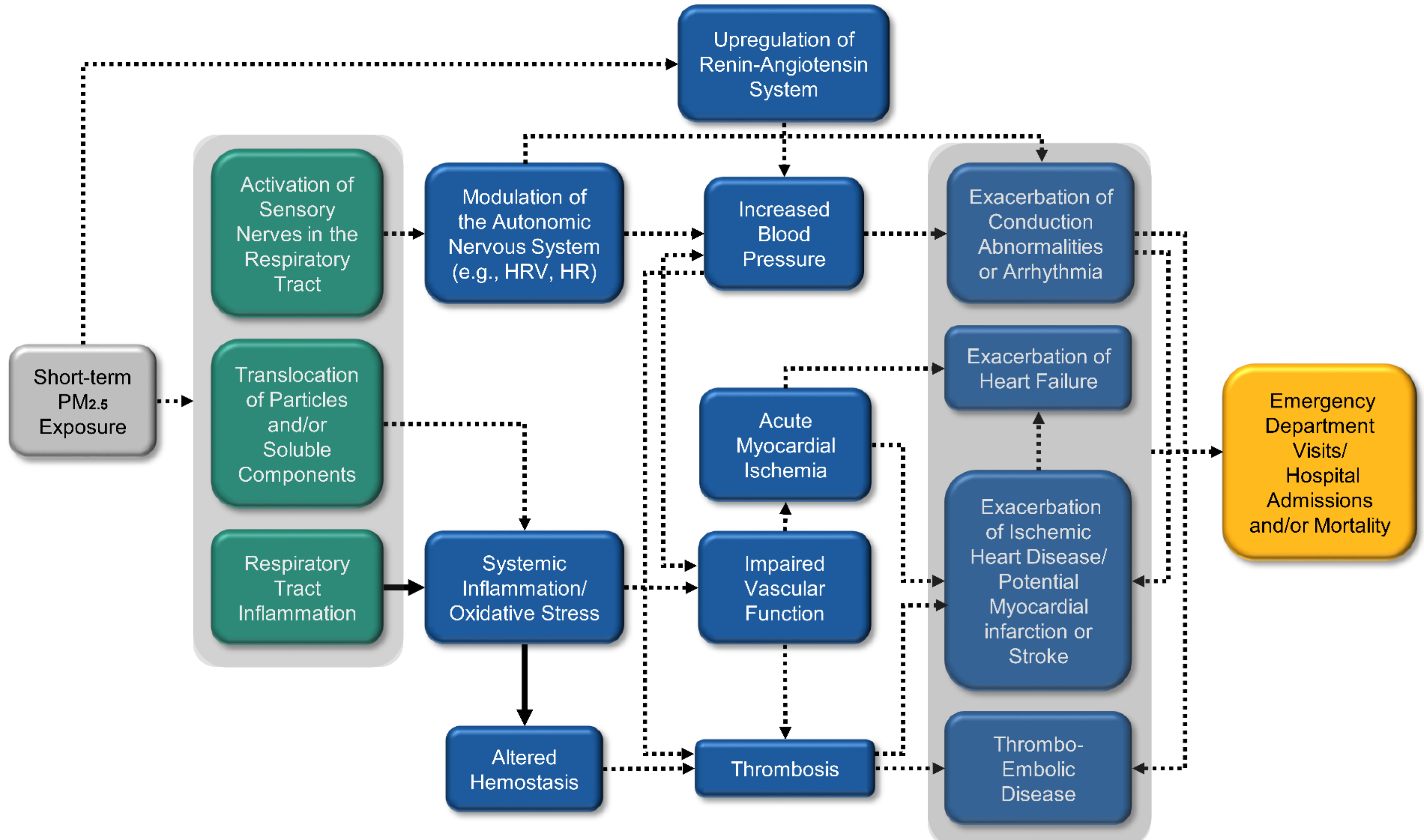
HUMAN HEALTH EFFECTS

		ISA	**Current PM Draft ISA**		
		Indicator	$PM_{2.5}$	$PM_{10-2.5}$	UFP
Health Outcome	Respiratory	Short-term exposure	▩	░	░
		Long-term exposure	▩	□	□
	Cardiovascular	Short-term exposure	■	░	░
		Long-term exposure	■	░ *	□
	Metabolic	Short-term exposure	░ *	□ *	□ *
		Long-term exposure	░ *	░ *	□ *
	Nervous System	Short-term exposure	░ *	□	░ *
		Long-term exposure	▩ *	░ *	▩ *
	Reproductive: Male/Female Reproduction and Fertility	Long-term exposure	░	□	□
	Reproductive: Pregnancy and Birth Outcomes	Long-term exposure	░	□	□
	Cancer	Long-term exposure	▩ *	░ *	□
	Mortality	Short-term exposure	■	░	□
		Long-term exposure	■	░ *	□

■ **Causal** ▩ **Likely causal** ░ **Suggestive** □ **Inadequate**

* = new determination or change in causality determination from 2009 PM ISA

Example: Potential Biological Pathways Figure



Short-term $PM_{2.5}$ Exposure

Activation of Sensory Nerves in the Respiratory Tract

Translocation of Particles and/or Soluble Components

Respiratory Tract Inflammation

Upregulation of Renin-Angiotensin System

Modulation of the Autonomic Nervous System (e.g., HRV, HR)

Systemic Inflammation/ Oxidative Stress

Altered Hemostasis

Increased Blood Pressure

Acute Myocardial Ischemia

Impaired Vascular Function

Thrombosis

Exacerbation of Conduction Abnormalities or Arrhythmia

Exacerbation of Heart Failure

Exacerbation of Ischemic Heart Disease/ Potential Myocardial infarction or Stroke

Thrombo-Embolic Disease

Emergency Department Visits/ Hospital Admissions and/or Mortality

Note: The boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Solid arrows denote direct evidence of the relationship as provided, for example, by an inhibitor of the pathway or a genetic knock-out model used in an experimental study. Shading around multiple boxes denotes relationships between groups of upstream and downstream effects. Progression of effects is depicted from left to right and color-coded (gray, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes. When there are gaps in the evidence, there are complementary gaps in the figure.

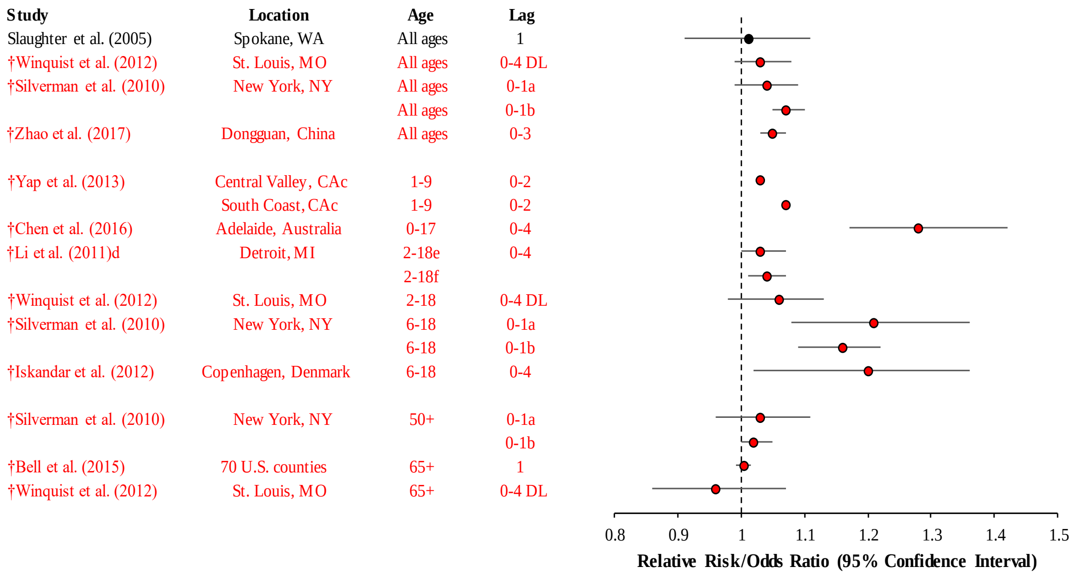
Respiratory Effects (Chapter 5)

Recent evidence supports the conclusions of the 2009 PM ISA, and continues to support a likely to be causal relationship between short- and long-term $PM_{2.5}$ exposure and respiratory effects

- Short-term $PM_{2.5}$ Exposure **(Likely to be Causal)**
  - Epidemiologic evidence: consistent evidence for asthma exacerbation in children and COPD exacerbation in adults, as well as respiratory mortality.
  - Experimental evidence: worsening of allergic airways disease and/or subclinical effects related to COPD, provide biological plausibility for asthma and COPD exacerbations
- Long-term $PM_{2.5}$ Exposure **(Likely to be Causal)**
  - Epidemiologic evidence: consistent changes in lung function and lung function growth rate, increased asthma incidence, asthma prevalence and wheeze in children; acceleration of lung function decline in adults; and respiratory mortality
  - Experimental evidence: impaired lung development and development of allergic airways disease, biological plausibility for decrements in lung function growth in children and asthma development

Respiratory Effects (Chapter 5)

Example: Short-term $PM_{2.5}$ Exposure and Asthma

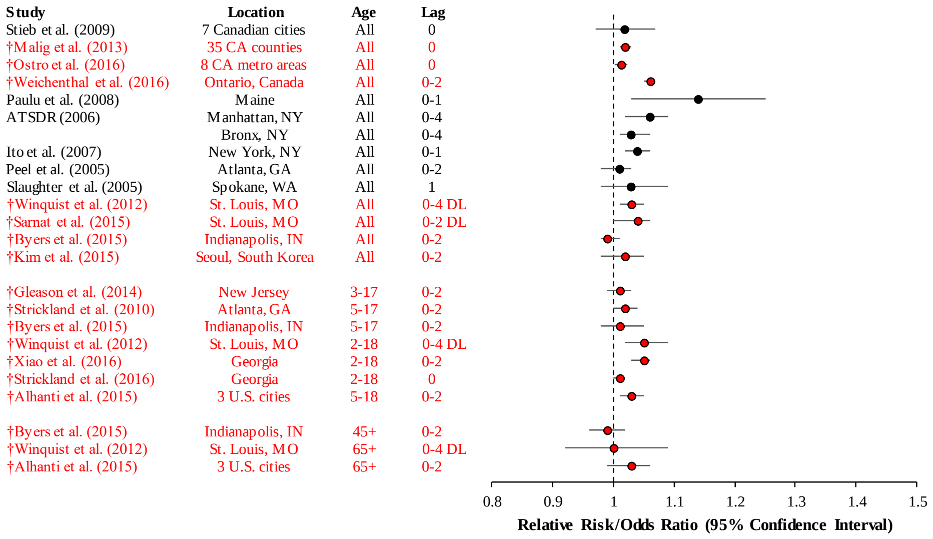


Hospital Admissions

Red = recent studies;
Black = U.S. study evaluated in the 2009 PM ISA

Emergency Department Visits

Red = recent studies;
Black = U.S. and Canadian studies evaluated in the 2009 PM ISA



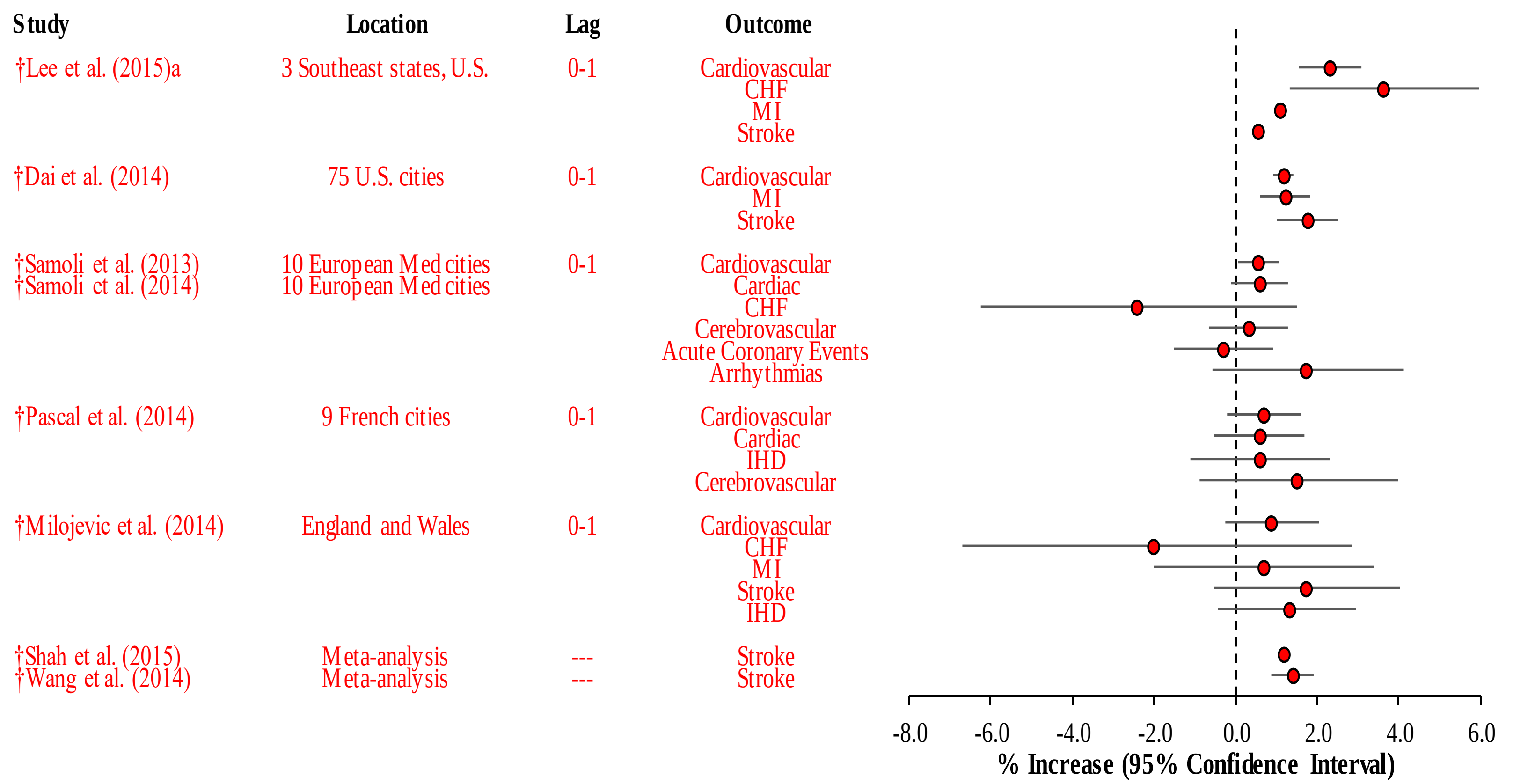
Cardiovascular Effects (Chapter 6)

A large body of recent evidence supports and extends the conclusions of the 2009 PM ISA that there is a causal relationship between short- and long-term PM$_{2.5}$ exposure and cardiovascular effects

- Short-term PM$_{2.5}$ Exposure **(Causal)**
  - Epidemiologic evidence: generally consistent positive associations for hospital admissions and ED visits, particularly for ischemic heart disease (IHD) and heart failure (HF), as well as cardiovascular mortality
  - Experimental evidence: endothelial dysfunction, effects indicating impaired cardiac function, arrhythmia, changes in heart rate variability (HRV), increases in blood pressure (BP), and indicators of systemic inflammation, oxidative stress, and coagulation
- Long-term PM$_{2.5}$ Exposure **(Causal)**
  - Epidemiologic evidence: consistent positive associations for cardiovascular mortality; evidence for coronary heart disease (CHD) and stroke particularly in populations with pre-existing disease; evidence for coronary artery calcification (CAC)
  - Experimental evidence: impaired heart function, increased blood pressure, endothelial dysfunction, and atherosclerotic plaque progression

Cardiovascular Effects (Chapter 6)

Example: Short-term $PM_{2.5}$ Exposure and Cardiovascular-related Mortality



Study	Location	Lag	Outcome
†Lee et al. (2015)a	3 Southeast states, U.S.	0-1	Cardiovascular
			CHF
			MI
			Stroke
†Dai et al. (2014)	75 U.S. cities	0-1	Cardiovascular
			MI
			Stroke
†Samoli et al. (2013)	10 European Med cities	0-1	Cardiovascular
†Samoli et al. (2014)	10 European Med cities		Cardiac
			CHF
			Cerebrovascular
			Acute Coronary Events
			Arrhythmias
†Pascal et al. (2014)	9 French cities	0-1	Cardiovascular
			Cardiac
			IHD
			Cerebrovascular
†Milojevic et al. (2014)	England and Wales	0-1	Cardiovascular
			CHF
			MI
			Stroke
			IHD
†Shah et al. (2015)	Meta-analysis	---	Stroke
†Wang et al. (2014)	Meta-analysis	---	Stroke

Red = recent studies

Figure 6-7. Percent increase in cause-specific cardiovascular mortality outcomes for a 10 μg/m³ increase in 24-hour average $PM_{2.5}$ concentrations observed in multicity studies and meta-analyses.

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Nervous System Effects (Chapter 8)

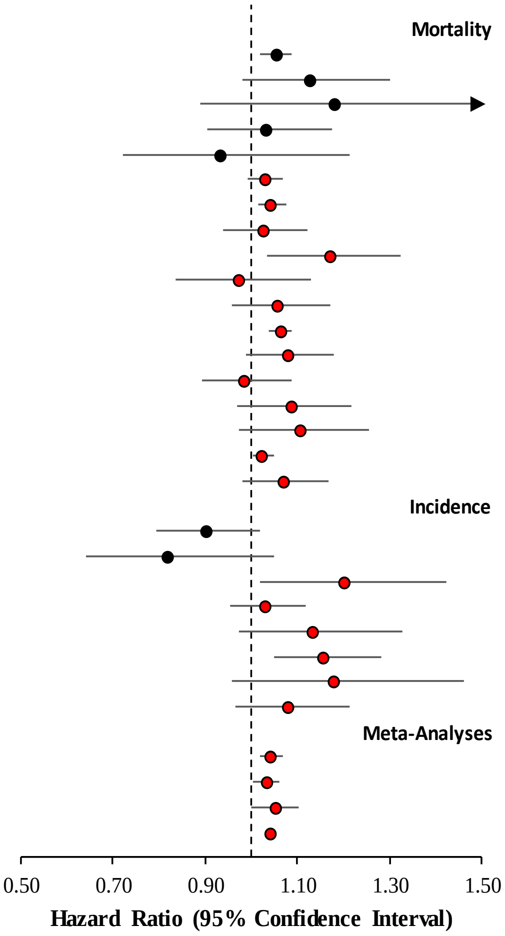
- Long-term $PM_{2.5}$ Exposure **(Likely to be Causal – NEW conclusion)**
  - Epidemiologic evidence
    - Consistent evidence for cognitive decline/impairment and decreased brain volume; more limited evidence for Alzheimer's disease and dementia
  - Experimental evidence
    - Consistent evidence for inflammation, oxidative stress, morphologic changes, and neurodegeneration in multiple brain regions of adult animals
    - Limited evidence for early indicators of Alzheimer's disease, impaired learning/memory, altered behavior in adult animals, and morphologic changes during development
- Long-term UFP Exposure **(Likely to be Causal – NEW conclusion)**
  - Epidemiologic evidence
    - Limited evidence for effects on cognitive development in children
  - Experimental evidence
    - Consistent evidence for inflammation, oxidative stress, and neurodegeneration in adult animals
    - Limited evidence of Alzheimer's disease pathology in a susceptible animal model
    - Strong evidence, mainly from one laboratory, for inflammation, morphologic changes including persistent ventriculomegaly, and behavioral effects following pre/postnatal exposure

Cancer (Chapter 10)

- Long-term $PM_{2.5}$ Exposure **(Likely to be Causal – NEW conclusion)**
  - Recent epidemiologic studies greatly expand upon the limited number of studies in the 2009 PM ISA that examined lung cancer incidence and mortality
    - Primarily positive associations, supported by analyses focusing on never smokers
  - Experimental and epidemiologic studies provide evidence for a relationship between $PM_{2.5}$ exposure and genotoxicity, epigenetic effects, and carcinogenic potential.
  - $PM_{2.5}$ exhibits several characteristics of carcinogens providing biological plausibility for $PM_{2.5}$ exposure contributing to cancer development

Cancer (Chapter 10)

Study	Cohort	Location	Follow-up Years	Qualifier
Krewski et al. (2009)	ACS (Re-analysis)	U.S.	1982-2000	
Laden et al. (2006)	HSC	6 U.S. cities	1974-1998	
McDonnell et al. (2000)	AHSMOG	California	1973-1977	Men
Brunekreef et al. (2009)a	NLCS - Air	Netherlands	1987-1996	Full Cohort
Brunekreef et al. (2009)a	NLCS - Air	Netherlands	1987-1996	Case Cohort
†Thurston et al. (2013)	ACS-CPS II	U.S.	1982-2004	
†Turner et al. (2016)	ACS-CPS II	U.S.	1982-2004	
†Hart et al. (2011)	TrIPS	U.S.	1985-2000	Men
†Lepeule et al. (2012)	HSC	6 U.S. cities	1974-2009	
†Lipsett et al. (2011)	CTS	California	2000-2005	Women
†Jerrett et al. (2013)	ACS-CPS II	California	1982-2000	
†Crouse et al. (2015)	CanCHEC	Canada	1991-2006	
†Pinault et al. (2016)	CCHS	Canada	2000-2011	
†Villeneuve et al. (2015)	CNBSS	Canada	1980-2005	Women
†Weichenthal et al. (2016)	CanCHEC	Ontario	1991-2009	
†Carey et al. (2013)	National English	United Kingdom	2003-2007	
†Cesaroni et al. (2013)	RoLS	Rome, Italy	2001-2010	
†Wong et al. (2016)	---	Hong Kong	1998-2011	
Brunekreef et al. (2009)b	NLCS - Air	Netherlands	1987-1996	Full Cohort
Brunekreef et al. (2009)b	NLCS - Air	Netherlands	1987-1996	Case Cohort
†Gharibvand et al. (2016)	AHSMOG-2	U.S.	2002-2011	
†Puett et al. (2014)	NHS	U.S.	1994-2010	Women
†Hystad et al. (2013)	NECSS	Canada	1994-1997	
†Tomczak et al. (2016)	CNBSS	Canada	1980-2004	Women
†Raaschou-Nielsen et al. (2013)	ESCAPE	Europe	1990s	
†Hart et al. (2015)	NCLS	Netherlands	1986-2003	
†Hamra et al. (2014)c	---	---	---	14 studies
†Yang et al. (2015)c	---	---	---	10 studies
†Chen et al. (2015)c	---	---	---	6 studies
†Cui et al. (2015)d	---	---	---	12 studies

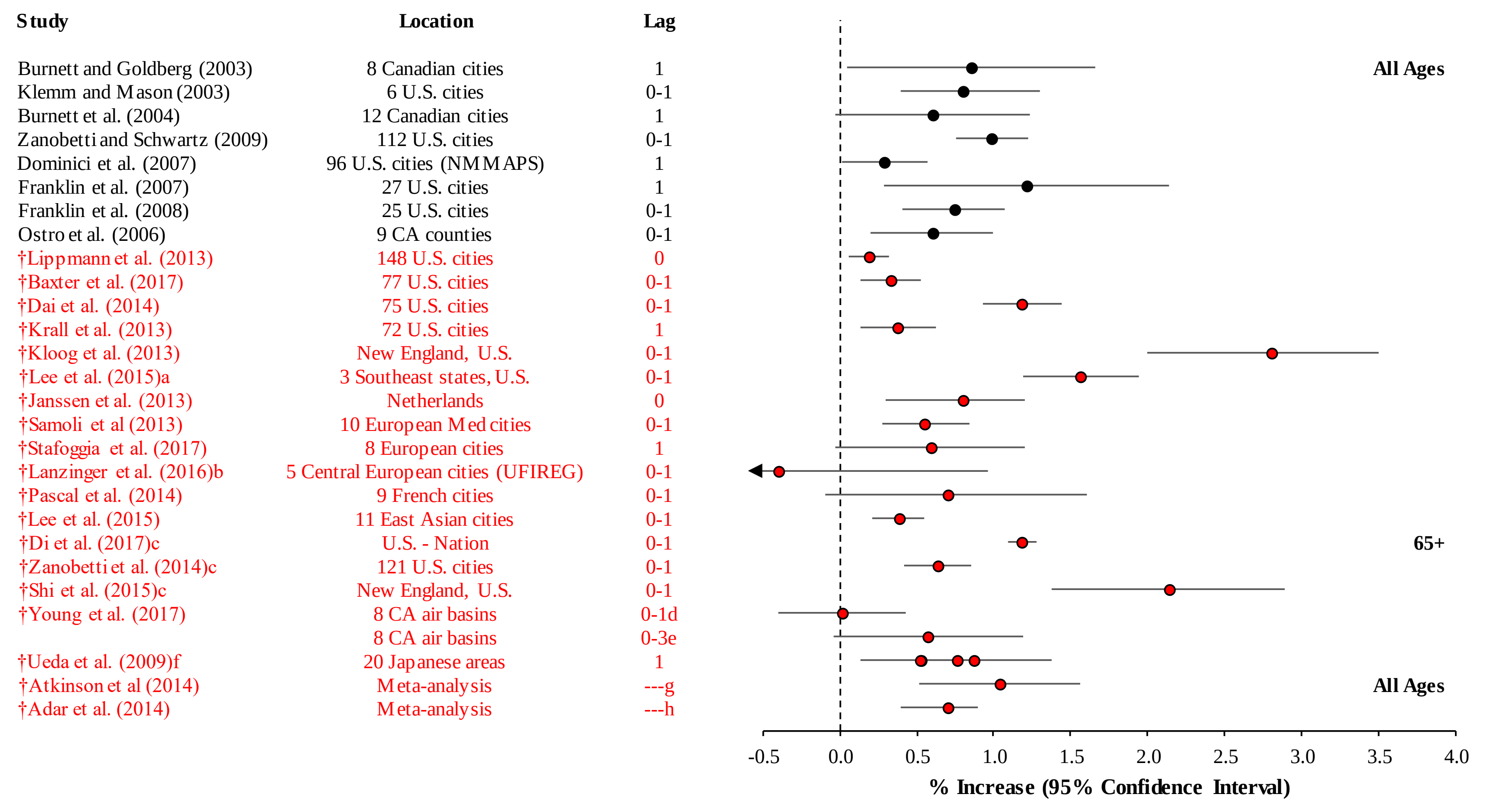


Note: Red = recent studies; Black = studies evaluated in the 2009 PM ISA

Figure 10-3. Summary of associations reported in previous and recent cohort studies that examined long-term $PM_{2.5}$ exposure and lung cancer mortality and incidence.

Mortality – Short-term PM$_{2.5}$ Exposure (Chapter 11) (Causal)

Recent evidence supports and extends the conclusions of the 2009 PM ISA that there is a causal relationship between short-term PM$_{2.5}$ exposure and mortality



Study	Location	Lag
Burnett and Goldberg (2003)	8 Canadian cities	1
Klemm and Mason (2003)	6 U.S. cities	0-1
Burnett et al. (2004)	12 Canadian cities	1
Zanobetti and Schwartz (2009)	112 U.S. cities	0-1
Dominici et al. (2007)	96 U.S. cities (NMMAPS)	1
Franklin et al. (2007)	27 U.S. cities	1
Franklin et al. (2008)	25 U.S. cities	0-1
Ostro et al. (2006)	9 CA counties	0-1
†Lippmann et al. (2013)	148 U.S. cities	0
†Baxter et al. (2017)	77 U.S. cities	0-1
†Dai et al. (2014)	75 U.S. cities	0-1
†Krall et al. (2013)	72 U.S. cities	1
†Kloog et al. (2013)	New England, U.S.	0-1
†Lee et al. (2015)a	3 Southeast states, U.S.	0-1
†Janssen et al. (2013)	Netherlands	0
†Samoli et al (2013)	10 European Med cities	0-1
†Stafoggia et al. (2017)	8 European cities	1
†Lanzinger et al. (2016)b	5 Central European cities (UFIREG)	0-1
†Pascal et al. (2014)	9 French cities	0-1
†Lee et al. (2015)	11 East Asian cities	0-1
†Di et al. (2017)c	U.S. - Nation	0-1
†Zanobetti et al. (2014)c	121 U.S. cities	0-1
†Shi et al. (2015)c	New England, U.S.	0-1
†Young et al. (2017)	8 CA air basins	0-1d
	8 CA air basins	0-3e
†Ueda et al. (2009)f	20 Japanese areas	1
†Atkinson et al (2014)	Meta-analysis	---g
†Adar et al. (2014)	Meta-analysis	---h

Note: Red = recent multi-city studies; Black = multi-city studies evaluated in the 2009 PM ISA

Figure 11-1. Summary of associations between short-term PM$_{2.5}$ exposure and total (nonaccidental) mortality in multicity studies for a 10 μg/m^3 increase in 24-hour average concentrations.

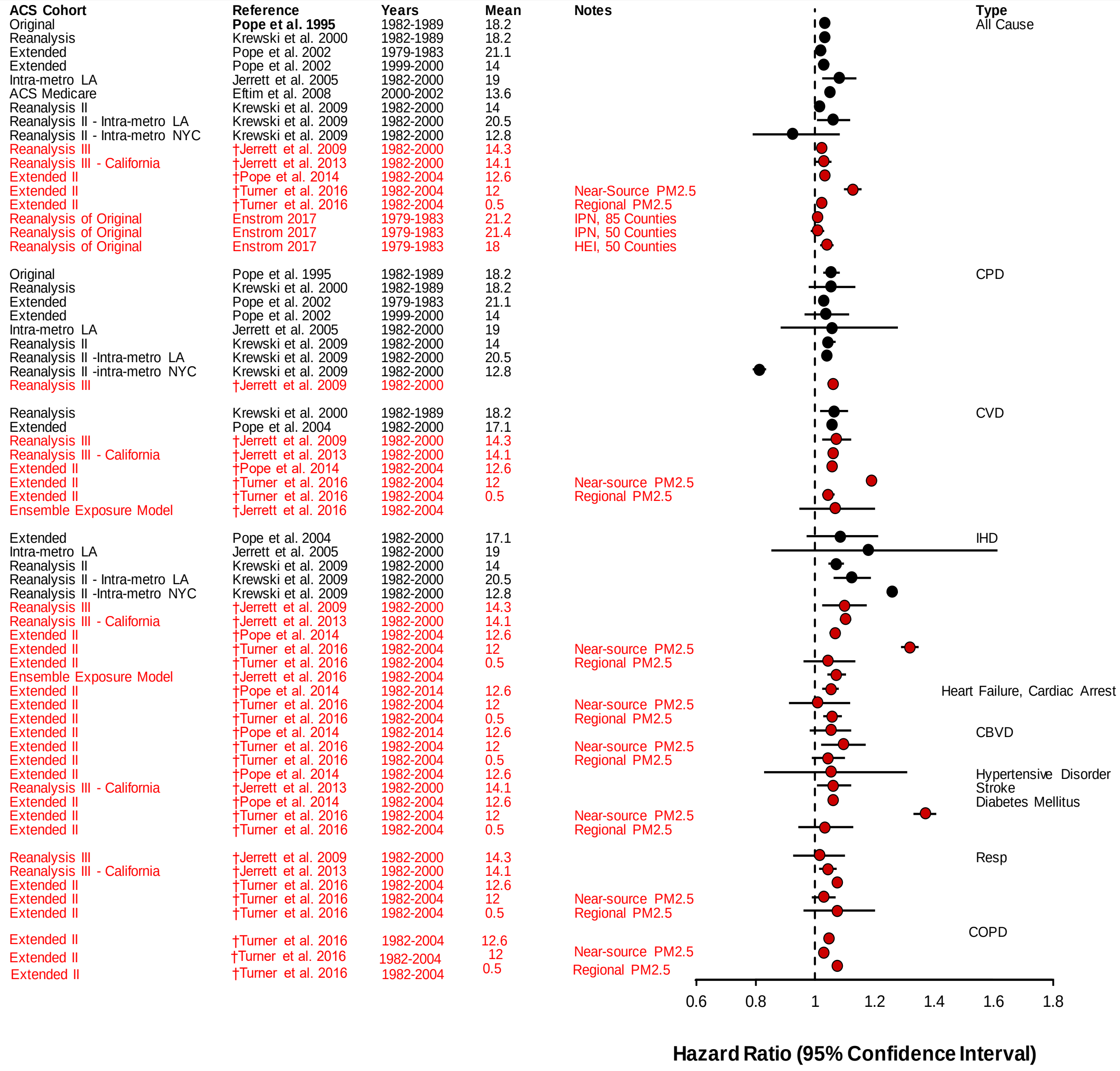
Mortality – Long-term $PM_{2.5}$ Exposure (Chapter 11) (Causal)

Recent evidence supports and extends the conclusions of the 2009 PM ISA that there is a causal relationship between long-term $PM_{2.5}$ exposure and mortality

Figure 11-17. Associations between long-term exposure to $PM_{2.5}$ and total (nonaccidental) mortality in the American Cancer Society (ACS) cohort.

Note: Associations are presented per 5 µg/m^3 increase in pollutant concentration.

Red = recent studies;
Black = studies evaluated in the 2009 PM ISA



ACS Cohort	Reference	Years	Mean	Notes	Type
Original	**Pope et al. 1995**	1982-1989	18.2		All Cause
Reanalysis	Krewski et al. 2000	1982-1989	18.2		
Extended	Pope et al. 2002	1979-1983	21.1		
Extended	Pope et al. 2002	1999-2000	14		
Intra-metro LA	Jerrett et al. 2005	1982-2000	19		
ACS Medicare	Eftim et al. 2008	2000-2002	13.6		
Reanalysis II	Krewski et al. 2009	1982-2000	14		
Reanalysis II - Intra-metro LA	Krewski et al. 2009	1982-2000	20.5		
Reanalysis II - Intra-metro NYC	Krewski et al. 2009	1982-2000	12.8		
Reanalysis III	†Jerrett et al. 2009	1982-2000	14.3		
Reanalysis III - California	†Jerrett et al. 2013	1982-2000	14.1		
Extended II	†Pope et al. 2014	1982-2004	12.6		
Extended II	†Turner et al. 2016	1982-2004	12	Near-Source PM2.5	
Extended II	†Turner et al. 2016	1982-2004	0.5	Regional PM2.5	
Reanalysis of Original	Enstrom 2017	1979-1983	21.2	IPN, 85 Counties	
Reanalysis of Original	Enstrom 2017	1979-1983	21.4	IPN, 50 Counties	
Reanalysis of Original	Enstrom 2017	1979-1983	18	HEI, 50 Counties	
Original	Pope et al. 1995	1982-1989	18.2		CPD
Reanalysis	Krewski et al. 2000	1982-1989	18.2		
Extended	Pope et al. 2002	1979-1983	21.1		
Extended	Pope et al. 2002	1999-2000	14		
Intra-metro LA	Jerrett et al. 2005	1982-2000	19		
Reanalysis II	Krewski et al. 2009	1982-2000	14		
Reanalysis II -Intra-metro LA	Krewski et al. 2009	1982-2000	20.5		
Reanalysis II -intra-metro NYC	Krewski et al. 2009	1982-2000	12.8		
Reanalysis III	†Jerrett et al. 2009	1982-2000			
Reanalysis	Krewski et al. 2000	1982-1989	18.2		CVD
Extended	Pope et al. 2004	1982-2000	17.1		
Reanalysis III	†Jerrett et al. 2009	1982-2000	14.3		
Reanalysis III - California	†Jerrett et al. 2013	1982-2000	14.1		
Extended II	†Pope et al. 2014	1982-2004	12.6		
Extended II	†Turner et al. 2016	1982-2004	12	Near-source PM2.5	
Extended II	†Turner et al. 2016	1982-2004	0.5	Regional PM2.5	
Ensemble Exposure Model	†Jerrett et al. 2016	1982-2004			
Extended	Pope et al. 2004	1982-2000	17.1		IHD
Intra-metro LA	Jerrett et al. 2005	1982-2000	19		
Reanalysis II	Krewski et al. 2009	1982-2000	14		
Reanalysis II - Intra-metro LA	Krewski et al. 2009	1982-2000	20.5		
Reanalysis II -Intra-metro NYC	Krewski et al. 2009	1982-2000	12.8		
Reanalysis III	†Jerrett et al. 2009	1982-2000	14.3		
Reanalysis III - California	†Jerrett et al. 2013	1982-2000	14.1		
Extended II	†Pope et al. 2014	1982-2004	12.6		
Extended II	†Turner et al. 2016	1982-2004	12	Near-source PM2.5	
Extended II	†Turner et al. 2016	1982-2004	0.5	Regional PM2.5	
Ensemble Exposure Model	†Jerrett et al. 2016	1982-2004			
Extended II	†Pope et al. 2014	1982-2014	12.6		Heart Failure, Cardiac Arrest
Extended II	†Turner et al. 2016	1982-2004	12	Near-source PM2.5	
Extended II	†Turner et al. 2016	1982-2004	0.5	Regional PM2.5	
Extended II	†Pope et al. 2014	1982-2014	12.6		CBVD
Extended II	†Turner et al. 2016	1982-2004	12	Near-source PM2.5	
Extended II	†Turner et al. 2016	1982-2004	0.5	Regional PM2.5	
Extended II	†Pope et al. 2014	1982-2004	12.6		Hypertensive Disorder
Reanalysis III - California	†Jerrett et al. 2013	1982-2000	14.1		Stroke
Extended II	†Pope et al. 2014	1982-2004	12.6		Diabetes Mellitus
Extended II	†Turner et al. 2016	1982-2004	12	Near-source PM2.5	
Extended II	†Turner et al. 2016	1982-2004	0.5	Regional PM2.5	
Reanalysis III	†Jerrett et al. 2009	1982-2000	14.3		Resp
Reanalysis III - California	†Jerrett et al. 2013	1982-2000	14.1		
Extended II	†Turner et al. 2016	1982-2004	12.6		
Extended II	†Turner et al. 2016	1982-2004	12	Near-source PM2.5	
Extended II	†Turner et al. 2016	1982-2004	0.5	Regional PM2.5	
Extended II	†Turner et al. 2016	1982-2004	12.6		COPD
Extended II	†Turner et al. 2016	1982-2004	12	Near-source PM2.5	
Extended II	†Turner et al. 2016	1982-2004	0.5	Regional PM2.5	

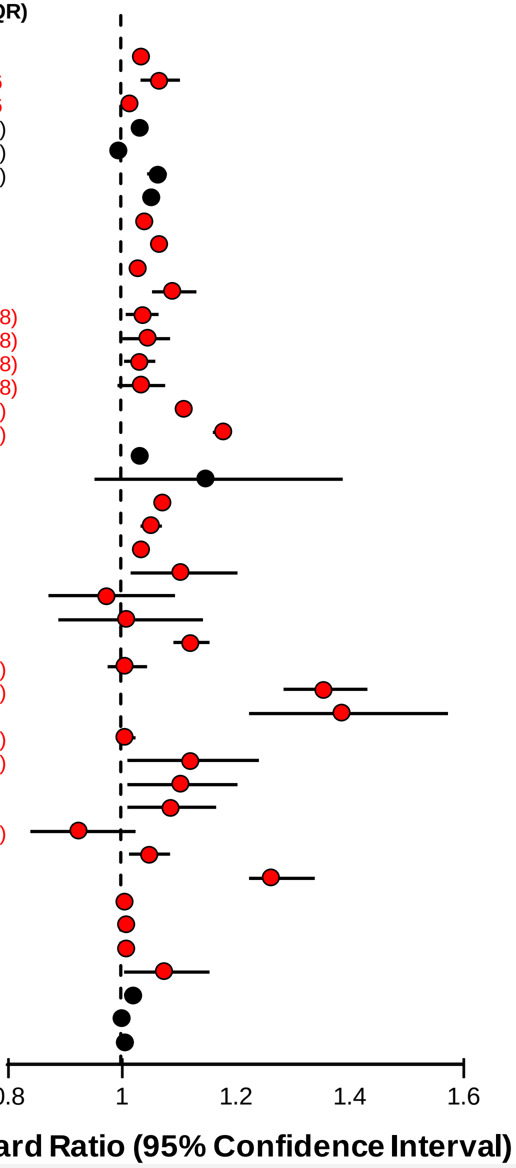
Mortality – Long-term PM$_{2.5}$ Exposure (Chapter 11) (Causal)

Figure 11-18. Associations between long-term PM$_{2.5}$ and total (nonaccidental) mortality in recent North American cohorts.

Note: Associations are presented per 5 µg/m^3 increase in pollutant concentration.

Red = recent studies;
Black = studies evaluated in the 2009 PM ISA

Reference	Cohort	Notes	Years	Mean (IQR)
†Pope et al. 2014	ACS		1982-2004	12.6
†Lepeule et al. 2012	Harvard Six Cities		1974-2009	11.4-23.6
†Thurston et al. 2015	NIH-AARP		2000-2009	10.2-13.6
Zeger et al. 2008	MCAPS	Eastern	2000-2005	14.0 (3.0)
Zeger et al. 2008	MCAPS	Western	2000-2005	13.1 (8.1)
Zeger et al. 2008	MCAPS	Central	2000-2005	10.7 (2.4)
Eftim et al. 2008	ACS-Medicare		2000-2002	13.6
†Di et al. 2017	Medicare		2000-2012	11.5
†Di et al. 2017	Medicare	exp<12	2000-2012	11.5
†Di et al. 2017	Medicare	nearest monitor	2000-2012	11.5
†Kioumourtzoglou et al. 2016	Medicare		2000-2010	12
†Shi et al. 2015	Medicare	mutual adj	2003-2008	8.12 (3.78)
†Shi et al. 2015	Medicare	exp <10, mutual adj	2003-2008	8.12 (3.78)
†Shi et al. 2015	Medicare	no mutual adj	2003-2008	8.12 (3.78)
†Shi et al. 2015	Medicare	exp <10, no mutual adj	2003-2008	8.12 (3.78)
†Wang et al. 2017	Medicare		2000-2013	10.7 (3.8)
†Wang et al. 2017	Medicare	exp<12	2000-2013	10.7 (3.8)
Lipfert et al. 2006	Veterans Cohort		1997-2001	14.34
Goss et al. 2004	U.S. Cystic Fibrosis		1999-2000	13.7
†Crouse et al. 2012	CanCHEC	Satellite data	1991-2001	8.9
†Crouse et al. 2012	CanCHEC	Monitor data	1991-2001	11.2
†Crouse et al. 2015	CanCHEC		1991-2006	8.9
†Chen et al. 2016	EFFECT		1999-2011	10.7
†Weichenthal et al. 2014	Ag Health		1993-2009	8.84
†Weichenthal et al. 2014	Ag Health	more precise exp	1993-2009	8.84
†Pinault et al. 2016	CCHS		1998-2011	6.3
†Lipsett et al. 2011	CA Teachers		2000-2005	15.6 (8.0)
†Ostro et al. 2010	CA Teachers	within 30 km	2002-2007	17.5 (6.1)
†Ostro et al. 2010	CA Teachers	within 8 km	2002-2007	17 (6.1)
†Ostro et al. 2015	CA Teachers		2001-2007	17.9 (9.6)
†Puett et al. 2009	Nurses Health		1992-2002	13.9 (3.6)
†Hart et al. 2015	Nurses Health	nearest monitor	2000-2006	12.7
†Hart et al. 2015	Nurses Health	spatio-temp. model	2000-2006	12
†Puett et al. 2011	Health Prof	full model	1989-2003	17.8 (4.3)
†Hart et al. 2011	TrIPS		1985-2000	14.1 (4)
†Kloog et al. 2013	MA cohort	CVD+Resp	2000-2008	9.9 (1.6)
†Garcia et al. 2015	CA cohort	Kriging	2006	13.06
†Garcia et al. 2015	CA cohort	IDW	2006	12.94
†Garcia et al. 2015	CA cohort	closest monitor	2006	12.68
†Wang et al. 2016	NJ Cohort		2004-2009	11.3
Enstrom 2005	CA Cancer Prev		1973-1982	23.4
Enstrom 2005	CA Cancer Prev		1983-2002	23.4
Enstrom 2005	CA Cancer Prev		1973-2002	23.4



Other Causality Determinations (Chapters 5 – 10)

- Limitations and uncertainties in the evidence, along with few or no epidemiologic and experimental studies resulted in conclusions of:
  - Suggestive of, but not sufficient to infer, a causal relationship, for:
    - $PM_{2.5}$: repro/dev, nervous system (ST)
    - $PM_{10-2.5}$: mortality (ST), respiratory (ST), cardiovascular (ST/LT), metabolic (LT), cancer, nervous system (LT)
    - UFP: respiratory (ST), cardiovascular, (ST), nervous system (ST).
  - Inadequate to determine the presence or absence of a causal relationship, for:
    - $PM_{10-2.5}$: respiratory (LT), metabolic (ST), repro/dev, nervous system (ST)
    - UFP: mortality (ST/LT), respiratory (LT), cardiovascular (LT), metabolic (ST/LT), repro/dev, cancer

Note: ST = short-term exposure; LT = long-term exposure

Policy-Relevant Considerations (Chapter 1)

- **Copollutant Confounding**: Across recent studies examining various health effects and both short- and long-term $PM_{2.5}$ exposures, associations remain relatively unchanged in copollutant models

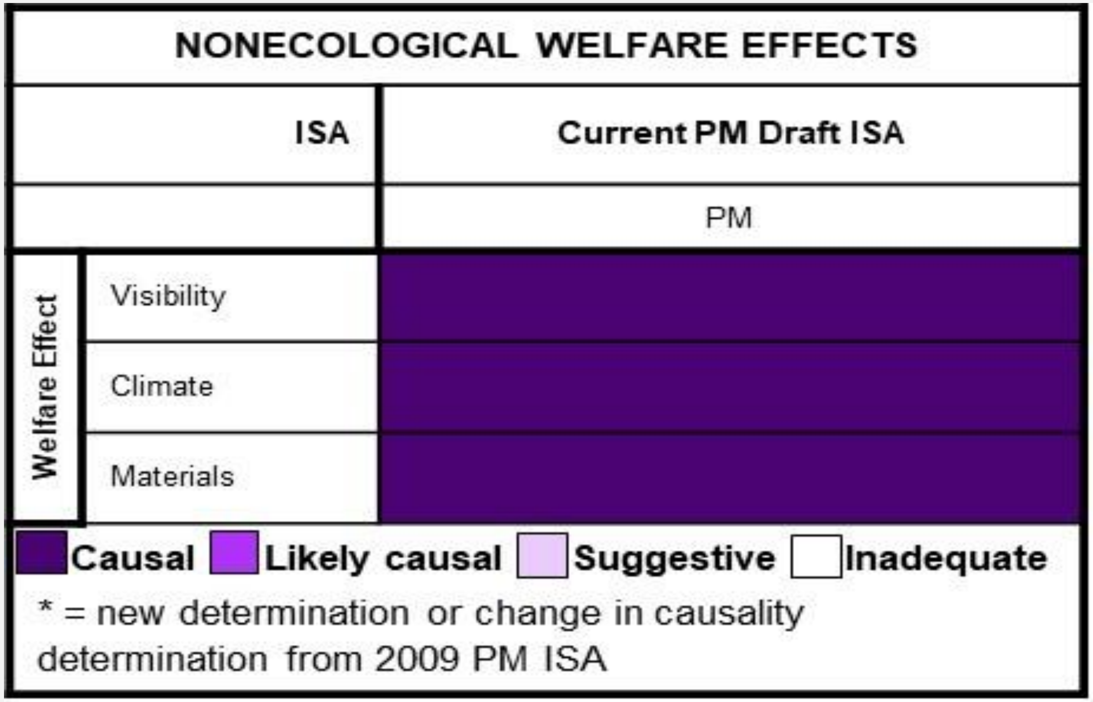
- **Concentration-Response (C-R) Relationship**: Across studies evidence continues to support a linear, no-threshold C-R relationship

- **PM Components and Sources**: 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 more strongly related with health effects than $PM_{2.5}$ mass

Populations Potentially at Increased Risk of a PM-related Health Effect (Chapter 12)

- The NAAQS are intended to protect both the population as a whole and those potentially at increased risk for health effects in response to exposure to criteria air pollutants
  - *Are there specific populations and lifestages at increased risk of a PM-related health effect, compared to a reference population?*
- The ISA identified and evaluated evidence for factors that may increase the risk of $PM_{2.5}$-related health effects in a population or lifestage, classifying the evidence into four categories:
  - Adequate evidence; suggestive evidence; inadequate evidence; evidence of no effect
- Conclusions:
  - Adequate: children and nonwhite populations
  - Suggestive: pre-existing cardiovascular and respiratory disease, overweight/obese, genetic variants glutathione pathways, low SES
  - Inadequate: pre-existing diabetes, older adults, residential location, sex, diet, and physical activity

Draft PM ISA
Welfare Effects: Causality Determinations



NONECOLOGICAL WELFARE EFFECTS		
	ISA	Current PM Draft ISA
		PM
Welfare Effect	Visibility	■
	Climate	■
	Materials	■

■ Causal 🟪 Likely causal ▨ Suggestive □ Inadequate

* = new determination or change in causality determination from 2009 PM ISA

Welfare Effects (Chapter 13)

Recent evidence supports and extends the conclusions of the 2009 PM ISA that there is a causal relationship between PM and welfare effects

- Visibility Impairment **(Causal)**
  - Long-term visibility improvements throughout the U.S as PM concentrations have decreased
  - Regional and seasonal patterns in atmospheric visibility parallel PM concentration patterns
  - More evidence supporting the relationship between visibility and PM composition
- Climate Effects **(Causal)**
  - New evidence provides greater specificity about radiative forcing
  - Increased understanding of additional climate impacts driven by PM radiative effects
  - Improved characterization of key sources of uncertainty particularly with response to PM-cloud interactions
- Materials Effects **(Causal)**
  - New information for glass and metals including modeling of glass soiling
  - Progress in the development of quantitative dose-response relationships and damage functions for materials in addition to stone, including glass and metals
  - Quantitative research on PM impacts on energy yield from photovoltaic systems

United States
Environmental Protection
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Supplemental Materials

May 2018 Memo: Standardized Charge Questions for CASAC

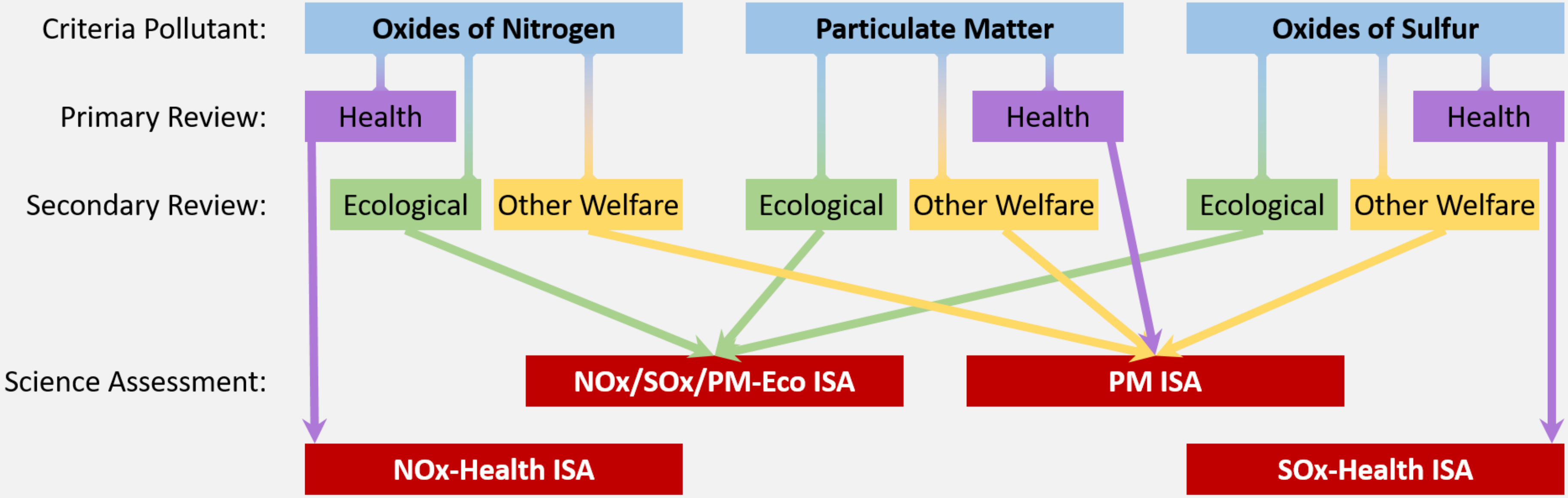
- The May 2018 memo identified general charge questions for CASAC in NAAQS reviews, to be supplemented with more detailed requests as necessary.
  - Are there areas in which additional knowledge is required to appraise the adequacy and basis of existing, new, or revised NAAQS? Please describe the research efforts necessary to provide the required information.
  - What scientific evidence has been developed since the last review to indicate if the current primary and/or secondary NAAQS need to be revised or if an alternative level or form of these standards is needed to protect public health and/or public welfare? Please recommend to the Administrator any new NAAQS or revisions of existing criteria and standards as may be appropriate. In providing advice, please consider a range of options for standard setting, in terms of indicators, averaging times, form, and ranges of levels for any alternative standards, along with a description of the alternative underlying interpretations of the scientific evidence and risk/exposure information that might support such alternative standards and that could be considered by the Administrator in making NAAQS decisions.
  - Do key studies, analyses, and assessments which may inform the Administrator's decision to revise the NAAQS properly address or characterize uncertainty and causality? Are there appropriate criteria to ensure transparency in the evaluation, assessment and characterization of key scientific evidence for this review?
- Two additional charge questions may elicit information not relevant to the standard-setting process. EPA may consider an appropriate mechanism, including after receiving CASAC’s final advice on the standards, to facilitate robust feedback on these topics.
  - What is the relative contribution to air pollution concentrations of natural as well as anthropogenic activity? In providing advice on any recommended NAAQS levels, please discuss relative proximity to peak background levels.
  - Please advise the Administrator of any adverse public health, welfare, social, economic, or energy effects which may result from various strategies for attainment and maintenance of such NAAQS.

NCEA/ORD and OAQPS/OAR Interactions:

NAAQS Review

NAAQS Activity	NCEA/ORD	OAQPS/OAR
Workshop on science-policy issues	Co-lead development	Co-lead development
Integrated Review Plan	Lead development of chapter on the ISA	Lead development of other chapters (e.g., REA, PA)
Integrated Science Assessment	Lead development	Review draft materials with focus on identifying areas where clarification is needed
Risk/Exposure Assessment	Review draft materials and provide comments on interpretation of science	Lead development
Policy Assessment	Review draft materials and provide comments on interpretation of science	Lead development
Rule-making materials	Provide technical and scientific support	Lead development

Relationship among Integrated Science Assessments



Criteria Pollutant: **Oxides of Nitrogen** | **Particulate Matter** | **Oxides of Sulfur**

Primary Review: Health | Health | Health

Secondary Review: Ecological | Other Welfare | Ecological | Other Welfare | Ecological | Other Welfare

Science Assessment: **NOx/SOx/PM-Eco ISA** | **PM ISA** | **NOx-Health ISA** | **SOx-Health ISA**

Notes: Primary (health-based) review of effects on public health = Health

Secondary (welfare-based) review of effects on pubic welfare = Ecological + Other Welfare

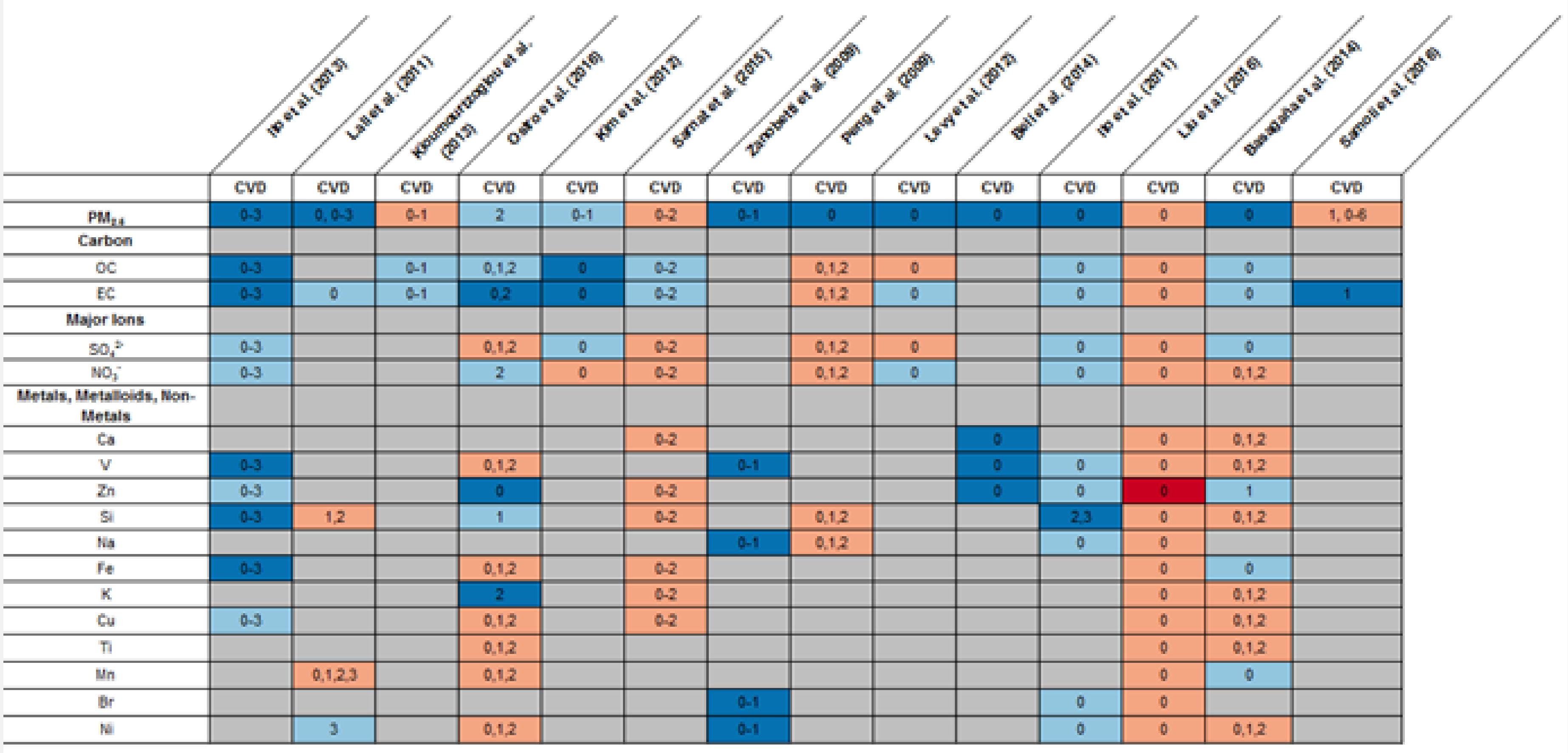
Ecological = effects on soil, water, crops, vegetation, animals, wildlife

Other Welfare = effects on manmade materials, weather, visibility, climate

EPA United States Environmental Protection Agency

Example: Evaluation of PM Components Studies

Short-term $PM_{2.5}$ and $PM_{2.5}$ Components Exposure and Cardiovascular Effects: Hospital Admissions and Emergency Department (ED) visits – Heat Map

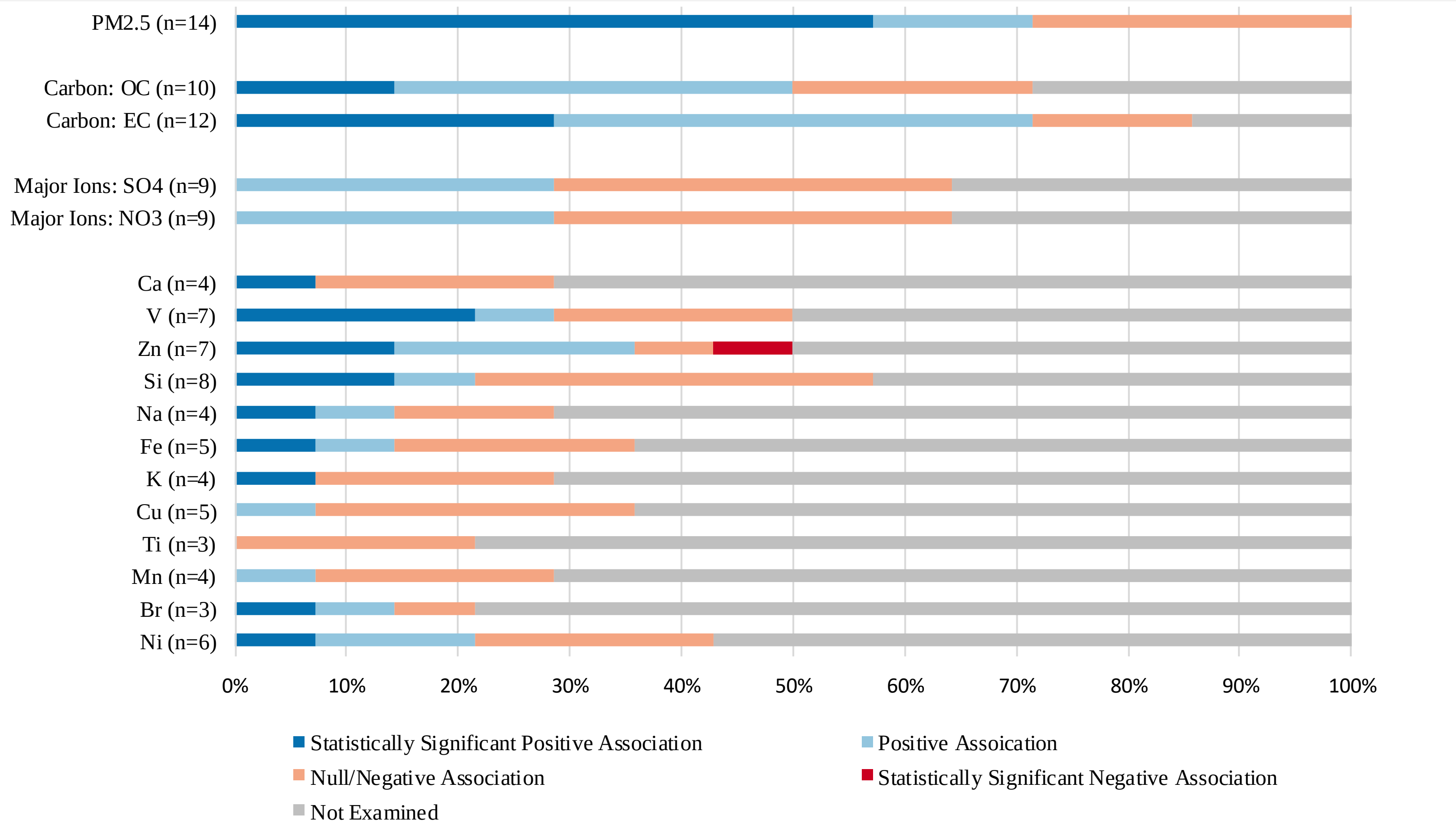


	Ito et al. (2013)	Lall et al. (2011)	Kioumourtzoglou et al. (2013)	Ostro et al. (2016)	Kim et al. (2012)	Sarnat et al. (2015)	Zanobetti et al. (2009)	Peng et al. (2009)	Levy et al. (2012)	Bell et al. (2014)	Ito et al. (2011)	Lin et al. (2016)	Basagaña et al. (2014)	Samoli et al. (2016)
	CVD	CVD	CVD	CVD	CVD	CVD	CVD	CVD	CVD	CVD	CVD	CVD	CVD	CVD
$PM_{2.5}$	0-3	0, 0-3	0-1	2	0-1	0-2	0-1	0	0	0	0	0	0	1, 0-6
Carbon														
OC	0-3		0-1	0,1,2	0	0-2		0,1,2	0		0	0	0	
EC	0-3	0	0-1	0,2	0	0-2		0,1,2	0		0	0	0	1
Major Ions														
SO_4^{2-}	0-3			0,1,2	0	0-2		0,1,2	0		0	0	0	
NO_3^-	0-3			2	0	0-2		0,1,2	0		0	0	0,1,2	
Metals, Metalloids, Non-Metals														
Ca						0-2				0		0	0,1,2	
V	0-3			0,1,2			0-1			0	0	0	0,1,2	
Zn	0-3			0		0-2				0	0	0	1	
Si	0-3	1,2		1		0-2		0,1,2			2,3	0	0,1,2	
Na							0-1	0,1,2			0	0		
Fe	0-3			0,1,2		0-2						0	0	
K				2		0-2						0	0,1,2	
Cu	0-3			0,1,2		0-2						0	0,1,2	
Ti				0,1,2								0	0,1,2	
Mn		0,1,2,3		0,1,2								0	0	
Br							0-1				0	0		
Ni		3		0,1,2			0-1				0	0	0,1,2	

- Numbers represent lags for which associations observed.
- $PM_{2.5}$ mass or $PM_{2.5}$ components associations categorized by results that are statistically significant positive (dark blue), positive/null (light blue), null/negative (light orange), statistically significant negative (red), or not examined (gray).

Example: Evaluation of PM Components Studies

Short-term $PM_{2.5}$ and $PM_{2.5}$ Components Exposure and Cardiovascular Effects: Hospital Admissions and ED visits – Distribution of Risk Estimates



Bars represent the percent of associations across studies for $PM_{2.5}$ mass or $PM_{2.5}$ components that are statistically significant positive (dark blue), positive (light blue), null/negative (light orange), statistically significant negative (red), or not examined (gray). n = number of studies that provided an estimate for $PM_{2.5}$ mass and individual $PM_{2.5}$ components.

At-Risk Framework Description

Classification	Health Effects
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 determine 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.

Excerpt from Preamble to ISAs