DRAFT 2016 AQMP
APPENDIX I

HEALTH EFFECTS

JULY 2016

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INTRODUCTION

This document presents a summary of scientific findings on the health effects of ambient air pollutants. The California Health and Safety Code Section 40471(b) requires that the South Coast Air Quality Management District (SCAQMD) prepare a report on the health impacts of particulate matter in the South Coast Air Basin (SCAB) in conjunction with the preparation of the Air Quality Management Plan (AQMP) revisions. This document, which was prepared to satisfy that requirement, also includes the health effects of the other major pollutants.

In addition to the air pollutant health effects summaries, there is an Attachment to this Appendix, which is a list of publications that have resulted from health-related research projects sponsored by SCAQMD over the past several years.

HEALTH EFFECTS OF AIR POLLUTION

Ambient air pollution is a major public health concern. Excess deaths and increases in illnesses associated with high air pollution levels have been documented in several episodes as early as 1930 in Meuse Valley, Belgium; 1948 in Donora, Pennsylvania; and 1952 in London. Although levels of pollutants that occurred during these acute episodes are now unlikely in the United States, ambient air pollution continues to be linked to increases in illness and other health effects (morbidity) and increases in death rates (mortality).

The adverse health effects associated with air pollution are diverse and include:

- Premature mortality
- Cardiovascular effects
- Increased health care utilization (hospitalization, physician and emergency room visits)
- Increased respiratory illness and other morbidity (symptoms, infections, and asthma exacerbation)
- Decreased lung function (breathing capacity)
- Lung inflammation

- Potential immunological changes
- Increased airway reactivity to a known pharmacological agent exposure--a method used in laboratories to evaluate the tendency of airways to have an increased possibility of developing an asthmatic response
- A decreased tolerance for exercise
- Adverse birth outcomes such as low birth weight
- Cancers

The evidence linking these effects to air pollutants is derived from population-based observational and field studies (epidemiological) as well as controlled laboratory studies involving human subjects and animals. There have been an increasing number of studies focusing on the mechanisms (that is, on learning how specific organs, cell types, and biomarkers are involved in the human body's response to air pollution) and specific pollutants responsible for individual effects. Yet the underlying biological pathways for these effects are not always clearly understood.

Although individuals inhale pollutants as a mixture under ambient conditions, the regulatory framework and the control measures developed are pollutant-specific for six major outdoor pollutants covered under Sections 108 and 109 of the Clean Air Act. This is appropriate, in that different pollutants can differ in their sources, their times and places of occurrence, the kinds of health effects they may cause, and their overall levels of health risk. Different pollutants, from the same or different sources, oftentimes occur together. Evidence for more than additive effects has not been strong and, as a practical matter, health scientists, as well as regulatory officials, usually must deal with one pollutant at a time in adopting air quality standards. To meet the air quality standards, comprehensive plans are developed such as the Air Quality Management Plan (AQMP); and to minimize exposure to toxic air contaminants in the South Coast AQMD, a local air toxics control plan is also prepared. These plans examine multiple pollutants, cumulative impacts, and transport issues related to attaining healthful air quality. A brief overview of the effects observed and attributed to various air pollutants is presented in this appendix.

This summary is drawn substantially from reviews presented previously (South Coast Air Quality Management District 1996; South Coast Air Quality Management District 2003; South Coast Air Quality Management District 2007; South Coast Air Quality

Management District 2013), and from the most recent U.S. EPA Integrated Science Assessment reviews for Ozone (U.S. EPA 2013b), Carbon Monoxide (U.S. EPA 2010), Particulate Matter (U.S. EPA 2009), Nitrogen Oxides (U.S. EPA 2016), Sulfur Dioxide (U.S. EPA 2008), and Lead (U.S. EPA 2013a). Additional reviews prepared by the California Air Resources Board and the California EPA Office of Environmental Health Hazard Assessment for Particulate Matter (California Air Resources Board and Office of Environmental Health Hazard Assessment 2002), for Ozone (California Air Resources Board and Office of Environmental Health Hazard Assessment 2005) and for Nitrogen Dioxide (California Air Resources Board and Office of Environmental Health Hazard Assessment 2007) were included in the summary. In addition, several large review articles on the health effects of air pollution also helped inform this appendix (American Thoracic Society 1996a; Brunekreef et al. 2002). This summary also draws upon a supplemental literature review of mortality and morbidity impacts of PM2.5, ozone, NO_2, and SO_2 conducted for the AQMP Socioeconomic Evaluation (Industrial Economics Inc. 2016b; Industrial Economics Inc. 2016a). This summary highlights studies that were conducted in the South Coast Air Basin or in Southern California, or alternatively, in California, if few studies from our local region are available on the specific topic. More detailed citations and discussions on air pollution health effects can be found in these references.[1]

Also included are tables showing summaries of the U.S. EPA conclusions regarding the causality of air pollution health effects. The table below shows the five descriptors used by the U.S. EPA for health effects.

TABLE I-1

Weight of Evidence Descriptions for Causal Determination of Health Effects

DETERMINATION	WEIGHT OF EVIDENCE
Causal Relationship	Evidence is sufficient to conclude that there is a causal relationship with relevant pollutant exposures. That is, the pollutant has been shown to result in health effects in studies in which chance, bias, and confounding could be ruled out with reasonable confidence. For example: (a) controlled human exposure studies that demonstrate consistent effects; or (b) observational studies that cannot be explained by plausible alternatives or are supported by other lines of evidence (e.g., animal studies or mode of action information). Evidence includes replicated and consistent high-quality studies by multiple investigators.

[1] Most of the studies referred to in this appendix are cited in the above sources. Only specific selected references to provide examples of the types of health effects are cited in this summary.

TABLE I-1 (Concluded)

Weight of Evidence Descriptions for Causal Determination

DETERMINATION	WEIGHT OF EVIDENCE
Likely To Be A Causal Relationship	Evidence is sufficient to conclude that a causal relationship is likely to exist with relevant pollutant exposures, but important uncertainties remain. That is, the pollutant has been shown to result in health effects in studies in which chance and bias can be ruled out with reasonable confidence but potential issues remain. For example: (a) observational studies show an association, but copollutant exposures are difficult to address and/or other lines of evidence (controlled human exposure, animal, or mode of action information) are limited or inconsistent; or (b) animal toxicological evidence from multiple studies from different laboratories that demonstrate effects, but limited or no human data are available. Evidence generally includes replicated and high-quality studies by multiple investigators.
Suggestive Of A Causal Relationship	Evidence is suggestive of a causal relationship with relevant pollutant exposures, but is limited because chance, bias, and confounding cannot be ruled out. For example, at least one high-quality epidemiologic study shows an association with a given health outcome but the results of other studies are inconsistent.
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.
Not Likely To Be A Causal Relationship	Evidence is suggestive of no causal relationship with relevant pollutant exposures. Several adequate studies, covering the full range of levels of exposure that human beings are known to encounter and considering susceptible populations, are mutually consistent in not showing an effect at any level of exposure.

(Adapted from U.S. EPA, 2009)

OZONE

Ozone is a gaseous air pollutant that is a highly reactive compound and a strong oxidizing agent. When ozone comes into contact with the respiratory tract, it can react with tissues and cause damage in the airways. Since it is a gas, ozone, or its reaction products, can penetrate into the gas exchange region of the deep lung.

In 1997, the U.S. EPA established the first federal standard for ozone averaged over 8 hours, at 0.08 ppm. In 2005, the California Air Resources Board (CARB) established standards of 0.09 ppm averaged over one hour and at 0.070 ppm averaged over eight hours. In 2008, the U.S. EPA lowered the federal standard for ozone to 0.075 ppm averaged over eight hours. On the basis of recent evaluations of ozone health effects, U.S. EPA's Clean Air Scientific Advisory Committee recommended in 2015 that the National Ambient Air Quality Standard (NAAQS) for ozone be reduced and recommended a range in which 0.070 ppm would be the upper limit. In 2015, the U.S. EPA concluded that the current national standard was not adequate to protect public health and lowered the 8-hour ozone standard to 0.070 ppm (U.S. EPA 2015b).

The tables below provide the overall U.S. EPA staff conclusions on the causality of short-term (i.e. hours, days, weeks) and long-term (i.e. months, years) ozone health effects for the health outcomes evaluated (U.S. EPA 2013b).

TABLE I-2

Summary of Causal Determinations for Short-Term Exposures to Ozone

HEALTH CATEGORY	CAUSAL DETERMINATION
Respiratory Effects	Causal relationship
Cardiovascular Effects	Likely to be a causal relationship
Central Nervous System Effects	Suggestive of a causal relationship
Effects on Liver and Xenobiotic Metabolism	Inadequate to infer a causal relationship
Effects on Cutaneous and Ocular Tissues	Inadequate to infer a causal relationship
Mortality	Likely to be a causal relationship

(From U.S. EPA, 2013a Table 1-1)

TABLE I-3

Summary of Causal Determinations for Long-Term Exposures to Ozone

HEALTH CATEGORY	CAUSAL DETERMINATION
Respiratory Effects	Likely to be a causal relationship
Cardiovascular Effects	Suggestive of a causal relationship
Reproductive and Developmental Effects	Suggestive of a causal relationship
Central Nervous System Effects	Suggestive of a causal relationship

Cancer	Inadequate to infer a causal relationship
Mortality	Suggestive of a causal relationship

(From U.S. EPA, 2013a Table 1-1)

Short-Term Exposure Effects of Ozone

The adverse effects reported with short-term ozone exposure are greater with increased activity because activity increases the breathing rate and the volume of air reaching the lungs, resulting in an increased amount of ozone reaching the lungs. Children are considered to be a particularly vulnerable population to air pollution effects because their lungs are still growing, they typically spend more time outdoors, are generally more physically active, and have a higher ventilation rate relative to their body weight, compared to adults.

A number of adverse health effects associated with ambient ozone levels have been identified from laboratory and epidemiological studies (American Thoracic Society 1996b; U.S. EPA 2006; U.S. EPA 2013b). These include increased respiratory symptoms, damage to cells of the respiratory tract, decrease in lung function, increased susceptibility to respiratory infection, an increased risk of hospitalization, and increased risk of mortality.

The results of several studies where human volunteers were exposed to ozone for 6.6 hours at levels between 0.04 and 0.12 ppm were summarized by Brown (Brown et al. 2008). As shown in Figure I-1, there is an increasing response on lung function with increasing exposure levels in moderately exercising subjects. A study published after the analysis by Brown et al. exposed healthy young adults for 6.6 hours under intermittent moderate exercise to each of the following: filtered air, and ozone at 0.06, 0.07, 0.08, and 0.87 ppm (Schelegle et al. 2009). The study found decreases in lung function (FEV1) with each of the different levels of ozone exposure, although the decrease in lung function at 0.06 ppm was not statistically different from exposure to filtered air. Lung function (FEV1) decreases were approximately 5%, 7%, and 11% at ozone exposure levels of 0.07, 0.08, and 0.87 ppm. A more recent study (Kim et al. 2011) exposed young healthy adults to 0.06 ppm ozone for 6.6 hours while engaging in intermittent moderate exercise, and found that the study participants exhibited an approximately 2% reduction in lung function (FEV1) and an increase in pulmonary inflammation after exposure.

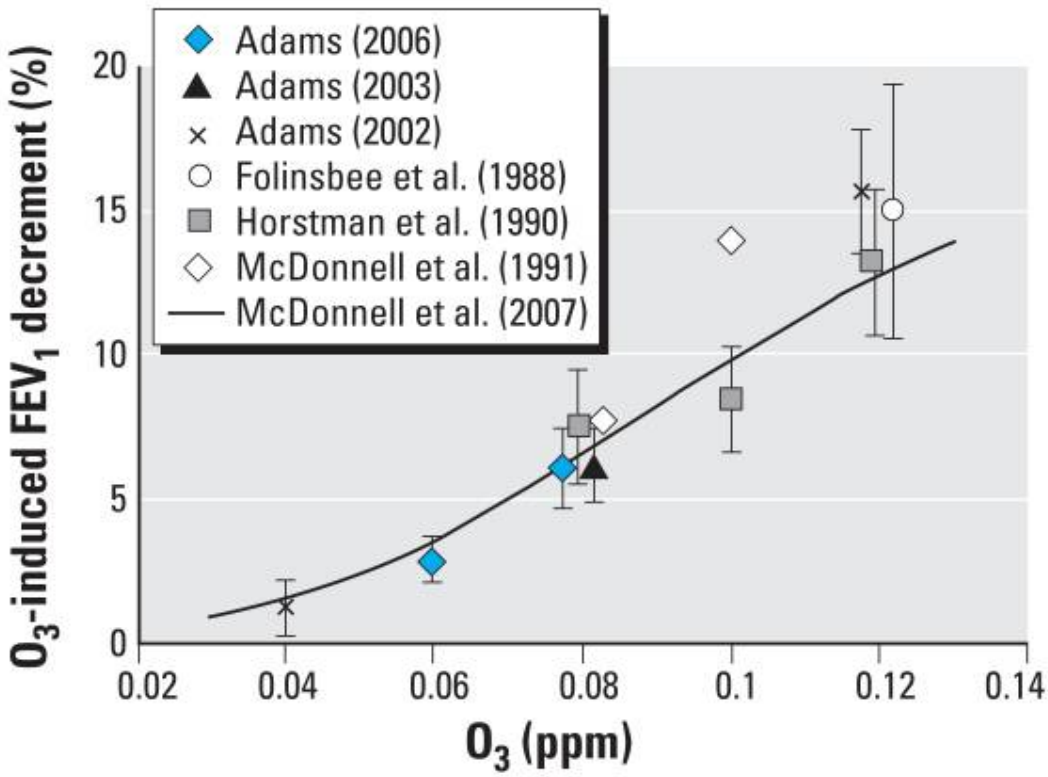


FIGURE I-1

Comparison of mean ozone-induced decrements in lung function following 6.6 hours of ozone exposure. Error bars are the standard error. (From: (Brown et al. 2008))

In addition to controlled laboratory conditions, studies of individuals exercising outdoors, including children attending summer camp, have shown associations of reduced lung function with ozone exposure. There were wide ranges in responses among individuals. U.S. EPA's recent review indicates that most studies found reductions in lung function (FEV_1) in the range of approximately <1 to 2% when standardized to an increase of 0.04 ppm for a 1-hour maximum, an increase of 0.03 ppm for an 8-hour maximum, and an increase of 0.02 ppm for a 24-hour average (U.S. EPA 2013b). Somewhat greater decrements in lung function (4.9 to 7.3%) were found in children with asthma who had respiratory infections or were using corticosteroid medication.

Increases in ozone levels are associated with increased numbers of absences from school. The Children's Health Study, conducted by researchers at the University of Southern California, followed for several years a cohort of children that live in 12 communities in Southern California with differing levels of air pollution. A publication from this study reported that school absences in fourth graders for

respiratory illnesses were positively associated with ambient ozone levels. An increase of 20 ppb (0.02 ppm) ozone was associated with a 63% increase in illness-related absence rates (95% confidence interval = 18%-124%) and an 83% increase in respiratory illnesses (95% confidence interval=4%-222%) (Gilliland et al. 2001).

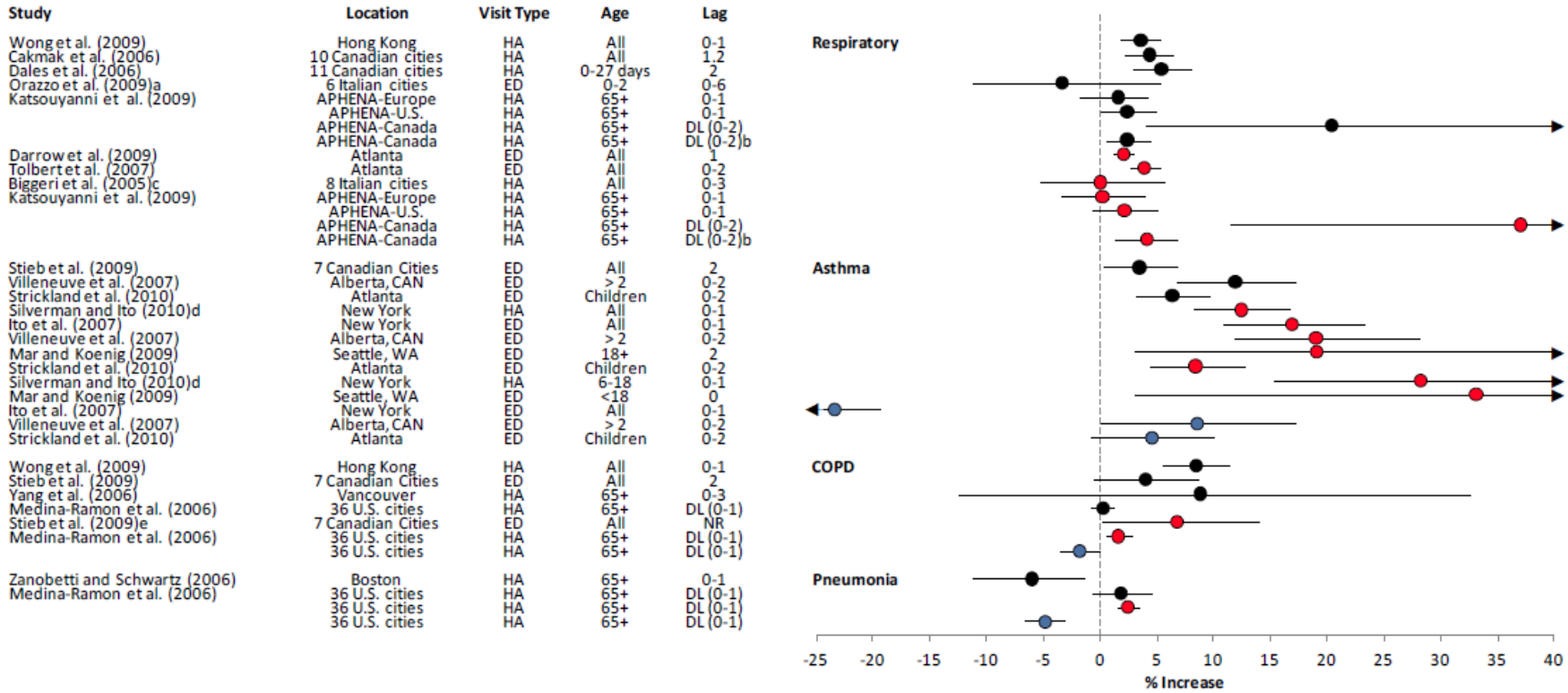
Some lung function responses (volume and airway resistance changes) observed after a single exposure to ozone exhibit attenuation or a reduction in magnitude with repeated exposures. Although it has been argued that the observed shift in response is evidence of a probable adaptation phenomenon, it appears that while functional changes may exhibit attenuation, biochemical and cellular changes which may be associated with episodic and chronic exposure effects may not exhibit an adaptation. That is, internal damage to the respiratory system may continue with repeated ozone exposures, even if externally observable effects (chest symptoms and reduced lung function) disappear. An additional argument against adaptation is that after several days or weeks without ozone exposures, the responsiveness (in terms of lung function as well as symptoms) returns.(U.S. EPA 2013b)

In the laboratory, exposure of human subjects to low levels of ozone causes reversible decreases in lung function as assessed by various measures such as respiratory volumes, airway resistance and reactivity, irritative cough and chest discomfort. Lung function changes have been observed with ozone exposure as low as 0.06 to 0.12 ppm for 6-8 hours under moderate exercising conditions (Horstman et al. 1990; Schelegle et al. 2009; Kim et al. 2011). The responses reported are indicative of decreased breathing capacity and are reversible.

Laboratory studies have also compared the degree of lung function change seen in healthy individuals versus asthmatics and those with chronic obstructive pulmonary disease (COPD). In several laboratory studies of individuals with COPD, the percent decreases in lung function from short-term ozone exposures ≤0.30ppm among patients with COPD generally did not differ from the lung function decrements experienced by healthy patients (Linn et al. 1982; Solic et al. 1982; Linn et al. 1983; Kehrl et al. 1985). That finding, however, may not accurately reflect the true impact of exposure on these respiration-compromised individuals. Since the respiration-compromised group may have lower lung function to begin with, the same total percent change in lung function may represent a substantially greater relative adverse effect overall. Other studies have found that subjects with asthma are more sensitive to the short-term effects of ozone in terms of lung function and inflammatory response, as evidenced by measuring changes in lung function, increased hospitalizations, and emergency room visits for

respiratory conditions (U.S. EPA 2013b). This evidence supports the hypothesis that asthmatics are a particularly sensitive population to the health effects of ozone.

Studies investigating the relationship between ozone exposure and hospital admissions and emergency room visits for all respiratory causes (infections, respiratory failure, chronic bronchitis, etc.) including asthma show a consistent increase as ambient ozone levels increase in a community. These excess hospital admissions and emergency room visits are observed when mean hourly ozone concentrations are as low as 0.06 to 0.10 ppm. Figure I-2 presents examples of studies regarding all-year and seasonal analysis of ozone exposure and respiratory morbidity.



Note: Effect estimates are for a 20 ppb increase in 24-hour; 30 ppb increase in 8-hour max; and 40 ppb increase in 1-hour max O_3 concentrations. HA=hospital admission; ED=emergency department. Black=All-year analysis; Red=Summer only analysis; Blue=Winter only analysis. (From (U.S. EPA 2013b) Figure 6-19)

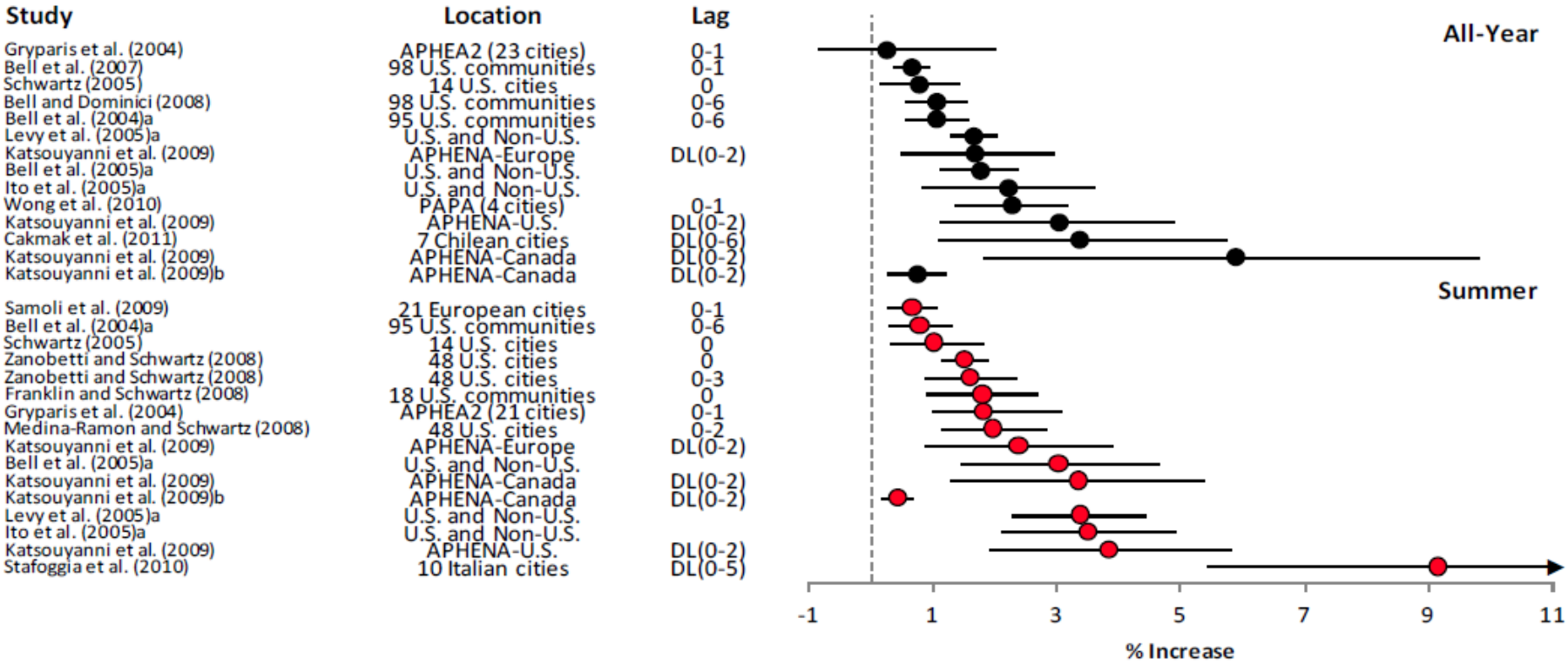
FIGURE I-2

Change in respiratory-related hospital admission and emergency department visits in studies that presented all-year and/or seasonal results.

Long-Term Exposure Effects of Ozone

Numerous studies have found positive associations between increases in ozone levels and excess risk of mortality (Bell et al. 2004; Bell et al. 2005; Huang et al. 2005; Ito et al. 2005; Levy et al. 2005; Bell et al. 2008; Zanobetti et al. 2008; Turner et al. 2016). These associations persist even when other variables including season and levels of particulate matter are accounted for, indicating that ozone mortality effects may be independent of other pollutants (Bell et al. 2004; Huang et al. 2005). A recent large-scale study similarly found increased risk of all-cause, cardiovascular, and respiratory mortality with ozone exposures, even after accounting for the effects of PM2.5 and NO_2, as well as other behavioral and demographic factors, including smoking (Turner et al. 2016). Other studies have found temperature to be an important potential risk factor for mortality, and may confound or modify the associations between air pollution exposure and mortality (Basu et al. 2002; Cheng et al. 2008). The Turner 2016 study examined the role of temperature, and found that the associations between ozone and mortality differed based on average daily maximum temperatures (Turner et al. 2016).

Examples of studies showing the relative change in mortality risks for all-year and summer only analyses are shown in Figure I-3.



Note: Effect estimates are for a 40 ppb increase in 1-hr max, 30 ppb increase in 8-hr max, and 20 ppb increase in 24-hr average O_3 concentrations. (From (U.S. EPA 2013b) Figure 6-27)

FIGURE I-3

Summary of mortality risk estimates for short-term O_3 exposure and all-cause (nonaccidental) mortality.

Results of epidemiology studies support the relationship between ozone exposure and respiratory effects. Several, but not all, studies have found associations of short-term ozone levels and hospital admissions and emergency department admissions for respiratory-related conditions (U.S. EPA 2013b). In a 2007 study conducted in Southern California, an increased risk of having poorly-controlled asthma was associated with higher long-term (annual average) ozone levels among men and elderly individuals (Meng et al. 2007).

In laboratory studies of animals, cellular and biochemical changes associated with respiratory tract inflammation have also been consistently found in the airway lining after low- level exposure to ozone. These changes include an increase in specific cell types and in the concentration of biochemical mediators of inflammation and injury such as Interleukin-1, Interleukin-6, Interleukin-8, Tumor Necrosis Factor α, and fibronectin (Van Bree et al. 2002; Johnston et al. 2007; U.S. EPA 2013b). Indications of lung injury and inflammatory changes have been observed in healthy adults exposed to ozone in the range of 0.06 to 0.10 ppm for up to 6.6 hours with intermittent moderate exercise (Kim et al. 2011).

Some animal studies show results that indicate possible chronic effects including functional and structural changes of the lung, although due to morphological, developmental, and immunological differences, it is difficult to apply these results to humans experiencing ambient exposures. These changes indicate that repeated inflammation associated with ozone exposure over a lifetime may result in cumulative damage to respiratory tissue such that individuals later in life may experience a reduced quality of life in terms of respiratory function and activity level achievable.(U.S. EPA 2013b) An autopsy study involving Los Angeles County residents who died between ages 14 and 25 years due to violent death, although conducted many years ago when pollutant levels were higher than currently measured, provided supportive evidence of lung tissue damage (structural changes), which the authors suggested were attributable to air pollution (Sherwin 1991), although many uncertainties remain about the extent to which air pollution explains the findings.

A publication from the Children's Health Study focused on children and outdoor exercise. In Southern California communities with high ozone concentrations, the relative risk of developing asthma in children playing three or more sports was found to be over three times higher than in children playing no sports (McConnell et al. 2002). These findings indicate that new cases of asthma in children may be associated with performance of heavy exercise in communities with high levels of ozone. While it has

long been known that air pollution can exacerbate symptoms in individuals with preexisting respiratory disease, this is among the first studies that indicate ozone exposure may contribute to asthma onset. However, three more recent Southern California studies did not find an association between ozone exposures and childhood asthma incidence, but did report increased risks of asthma onset with higher exposures to particulate matter or NO_2 (Islam et al. 2007; McConnell et al. 2010; Nishimura et al. 2013).

A study of birth outcomes in Southern California found an increased risk for birth defects in the aortic and pulmonary arteries associated with ozone exposure in the second month of pregnancy (Ritz et al. 2002). This was the first study linking ambient air pollutants to birth defects in humans. Studies conducted since mostly focusing on cardiac and oral cleft defects have found mixed results, with some showing associations, but others did not. Similarly, several studies have examined the impact of prenatal air pollution exposures and low birth weight or birth weight reductions, but the results for ozone effects on this health endpoint are mixed (Ritz et al. 2007; Morello-Frosch et al. 2010; Trasande et al. 2013; Laurent et al. 2014; Symanski et al. 2016). A couple of newer studies have examined ozone effects on stillbirth, often defined as the death of a fetus after at least 20 weeks of gestation (Hwang et al. 2011; Green et al. 2015). One of these studies was conducted in California, and found that third trimester ozone exposures were associated with increased risk of stillbirth, even after accounting for PM2.5 and NO_2 exposures (Green et al. 2015).

In addition to stillbirth, other newer health endpoints assessed in recent studies evaluating ozone exposures include autism, cardiovascular disease, hypertensive disorder of pregnancy, and gestational diabetes. One study of childhood autism was conducted in Los Angeles County and reported increased odds of developing autism with higher prenatal exposures to NO_x and ozone (Becerra et al. 2013). Three recent studies examined ozone effects on cardiovascular disease, with two studies reporting positive associations (Koken et al. 2003; Ensor et al. 2013) and one study reporting no evidence of an association (Rodopoulou et al. 2014). Two studies examined pregnancy-related conditions, with one study reporting a link between ozone exposures in the second trimester and hypertensive disorders of pregnancy (Mobasher et al. 2013) and another study reporting that first trimester ozone exposures were negatively associated with gestational diabetes risk, while second trimester ozone exposures and preconception SO_2 exposures increased gestational diabetes risk (Robledo et al. 2015). These studies represent emerging areas of research, where limited evidence is currently available to assess causality.

Sensitive Populations for Ozone-Related Health Effects

A number of population groups are potentially at increased risk for ozone exposure effects. In the review of ozone health effects, the U.S. EPA has identified several populations as having adequate evidence for increased risk from ozone exposures. These include children, older adults, outdoor workers, and individuals with asthma, lower socioeconomic status, or reduced intake of certain nutrients such as Vitamins C and E (Kreit et al. 1989; Horstman et al. 1995; Sienra-Monge et al. 2004; Romieu et al. 2012; U.S. EPA 2013b; Bell et al. 2014). There is suggestive evidence for other potential factors, such as variations in genes related to oxidative metabolism or inflammation, gender, socioeconomic status, and obesity (U.S. EPA 2013b). However, further evidence is needed.

Summary – Ozone Health Effects

In summary, adverse effects associated with ozone exposures have been well documented, with strong evidence supporting a link to respiratory effects. Although the specific mechanisms of action for ozone effects on the various health endpoints have not been fully identified, there is evidence of the important roles of oxidation of key enzymes and proteins, inflammatory responses, changes in immune response, and modification and activation of neural reflex pathways (U.S. EPA 2013b).

PARTICULATE MATTER

Airborne particulates are a complex group of pollutants that vary in source, size, and composition, depending on location, time, and meteorological conditions. The components include nitrates, sulfates, elemental carbon, organic carbon compounds, acid aerosols, trace metals, and material from the earth's crust. Substances of biological origin, such as pollen and spores, are also present.

The National Ambient Air Quality Standard for particulate matter was established in 1971, and set limits on the ambient level of Total Suspended Particulates (TSP). In 1987, the national particulate matter standards were revised to cover particles sized 10 μm (micrometers) aerodynamic diameter and smaller. These can be inhaled through the upper airways and deposited in the lower airways and gas exchange tissues in the lung. These particles are referred to as PM10. U.S. EPA initially promulgated ambient air quality standards for PM10 of 150 $\mu g/m^3$ averaged over a 24-hour period, and 50

μg/m^3 for an annual average. U.S. EPA has since rescinded the annual PM10 standard, but kept the 24-hour standard.

In more recent years, additional focus has been placed on particles having an aerodynamic diameter of 2.5 μm or less (PM2.5). A greater fraction of particles in this size range can penetrate and deposit deep in the lungs. The U.S. EPA established standards for PM2.5 in 1997 and in 2006 lowered the air quality standards for PM2.5 to 35 μg/m^3 for a 24-hour average and reaffirmed 15 μg/m^3 for an annual average standard. There was considerable controversy and debate surrounding the review of particulate matter health effects and the consideration of ambient air quality standards (Kaiser 1997; Vedal 1997) when the U.S. EPA promulgated the initial PM2.5 standards in 1997. The California Air Resources Board adopted an air quality standard for PM2.5 in 2002 at 12 μg/m^3 annual average.

Since that time, numerous studies have been published and some of the key studies were closely scrutinized and the data reanalyzed by additional investigators. The reanalyses confirmed the original findings, and there are now additional data confirming and extending the range of the adverse health effects of PM2.5 exposures. In 2012, the U.S. EPA revised the PM2.5 annual average standard to 12.0 μg/m^3 (U.S. EPA 2013c).

There have been several reviews of the health effects of ambient particulate matter (American Thoracic Society 1996a; Brunekreef et al. 2002; U.S. EPA 2004; U.S. EPA 2009; Brook et al. 2010). In addition, the California Air Resources Board (CARB) and the Office of Environmental Health and Hazard Assessment (OEHHA) have reviewed the adequacy of the California Air Quality Standards for Particulate Matter (California Air Resources Board and Office of Environmental Health Hazard Assessment 2002).

The major types of health effects associated with particulate matter include:

- Increased mortality
- Exacerbation of respiratory disease and of cardiovascular disease as evidenced by increases in:
    - Respiratory symptoms, exacerbation of asthma
    - Cardiovascular symptoms, non-fatal myocardial infarction
    - Hospital admissions and emergency room visits
    - Physician office visits

- School absences

- Adverse birth outcomes
- Effects on lung function
- Changes in lung morphology

In the 2009 Integrated Science Assessment for Particulate Matter, the U.S. EPA presented conclusions on the particulate matter causal determination of several health effects based on an updated review of scientific studies (U.S. EPA 2009). The conclusions are presented separately for particulates in the size range of 2.5 to 10 micrometers (μm) in aerodynamic diameter (PM10-2.5, often referred to as the coarse fraction) and those ≤2.5 μm (PM2.5, or fine particles). Of note, there is currently no federal or California standard for PM10-2.5. These conclusions are depicted in the following tables.

TABLE I-4

Summary of Causal Determination of PM10-2.5 by Exposure Duration and Health Outcome

SHORT-TERM EXPOSURES	
Health Outcome	**Causality Determination**
Cardiovascular effects	Suggestive of a causal relationship
Respiratory effects	Suggestive of a causal relationship
Mortality	Suggestive of a causal relationship

LONG-TERM EXPOSURES	
Health Outcome	**Causality Determination**
Cardiovascular effects	Inadequate to infer a causal relationship
Respiratory effects	Inadequate to infer a causal relationship
Mortality	Inadequate to infer a causal relationship
Reproductive and developmental	Inadequate to infer a causal relationship

(From (U.S. EPA 2009) Table 2-3 and Section 2.3.4)

TABLE I-5

Summary of Causal Determination of PM2.5 by Exposure Duration and Health Outcome

SHORT-TERM EXPOSURES	
Health Outcome	**Causality Determination**

Cardiovascular effects	Causal relationship
Respiratory effects	Likely to be a causal relationship
Central nervous system	Inadequate to infer a causal relationship
Mortality	Causal relationship
LONG-TERM EXPOSURES	
Health Outcome	**Causality Determination**
Cardiovascular effects	Causal relationship
Respiratory effects	Likely to be a causal relationship
Mortality	Causal relationship
Reproductive and developmental	Suggestive of a causal relationship
Cancer, Mutagenicity, Genotoxicity	Suggestive of a causal relationship

(From (U.S. EPA 2009) Tables 2-1 and 2-2)

There are also differences in the composition and sources of particles in the different size ranges that may have implications for health effects. The particles in the coarse fraction (PM10-2.5) are mostly produced by mechanical processes. These include automobile tire wear, industrial processes such as cutting and grinding, and resuspension of particles from the ground or road surfaces by wind and human activities, such as agricultural, mining, and construction operations, which may be particularly important in rural areas.

In contrast, particles smaller than 2.5 μm are mostly derived from combustion sources, such as automobiles, trucks, and other vehicle exhaust, as well as from stationary combustion sources. The particles are either directly emitted or are formed in the atmosphere from gases that are emitted. Components from material in the earth's crust, such as dust, are also present, with the amount varying in different locations.

Attention to another range of very small particles has been increasing over the last several years. These are generally referred to as "ultrafine" particles, with diameters of 0.1 μm or less. Ultrafine particles are mainly composed of particles from fresh emissions of combustion sources, but are also formed in the atmosphere by condensation of vapors that are emitted or by chemical or photochemical reactions with other contaminants in the air.

Ultrafine particles have relatively short half-lives (minutes to hours) and the particle size rapidly grows through condensation and coagulation processes into particles

within the PM2.5 size range. Ultrafine particles are garnering interest since a limited number of epidemiological and some laboratory studies, though not all, indicate that their toxicity may be higher on a mass basis than larger particles. There is also evidence that these small particles, or toxic components carried on their surface, can translocate from the lung to the blood and to other organs of the body, or through the olfactory bulb into the brain (U.S. EPA 2009). Currently, there are no federal or California standards for ultrafine particles. As such, the health effects of ultrafine particles is discussed in a separate section following the discussion of PM10 and PM2.5.

The current federal and California standards for particulate matter are listed in Table I-6.

TABLE I-6

Ambient Air Quality Standards for Particulate Matter

STANDARD	FEDERAL	CALIFORNIA
PM10 24-Hour average	150 $\mu g/m^3$	50 $\mu g/m^3$
PM10 Annual Average	--	20 $\mu g/m^3$
PM2.5 24-Hour Average	35 $\mu g/m^3$	--
PM2.5 Annual Average	12 $\mu g/m^3$	12 $\mu g/m^3$

Short-Term Exposure Effects of PM

Epidemiological studies have provided evidence for most of the effects listed above. In an extensive report focusing on the history of particulate matter research, the U.S. EPA reviewed several well-conducted studies that reported an association between mortality and increased daily or several-day-average concentrations of PM10 (U.S. EPA 2004). In addition, excess mortality and morbidity are reported in many studies involving communities across the U.S. as well as in Europe, Asia, and South America (Lu et al. 2015; Shah et al. 2015; Cai et al. 2016). A review and analysis of epidemiological literature for acute adverse effects of particulate matter was published by the American Thoracic Society in 1996, where several adverse effects were listed as associated with daily PM10 exposures (Table I-7). The review also reported that individuals who are elderly or have preexistent lung or heart disease are more susceptible than others to the adverse effects of PM10 (American Thoracic Society 1996a).

TABLE I-7

Combined Effect Estimates of Daily Mean Particulate Pollution (PM10)

	% CHANGE IN HEALTH INDICATOR PER EACH 10 μg/m^3 INCREASE IN PM10
Increase in Daily Mortality	
Total deaths	1.0
Respiratory deaths	3.4
Cardiovascular deaths	1.4
Increase in Hospital Usage (all respiratory diagnoses)	
Admissions	1.4
Emergency department visits	0.9
Exacerbation of Asthma	
Asthmatic attacks	3.0
Bronchodilator use	12.2
Emergency department visits*	3.4
Hospital admissions	1.9
Increase in Respiratory Symptom Reports	
Lower respiratory	3.0
Upper respiratory	0.7
Cough	2.5
Decrease in Lung Function	
Forced expiratory volume	0.15
Peak expiratory flow	0.08

* One study only
(From: (American Thoracic Society 1996a))

Since then, many more recent studies have provided additional evidence that excess mortality and morbidity are associated with short-term exposure to PM10 and PM2.5 (Pope et al. 2006).

Estimates of mortality effects from studies of PM10 exposures range from 0.3 to 1.7% increase for a 10 μg/m^3 increase in PM10 levels. The National Morbidity, Mortality, and Air Pollution Study (NMMAPS), a study of 20 of the largest U.S. cities, determined a combined risk estimate of about a 0.5% increase in total mortality for a

10 μg/m^3 increase in PM10 (Samet et al. 2000a). This study also analyzed the effects of gaseous co-pollutants. The results indicated that the association of PM10 and mortality was not strongly confounded by the presence of these co-occuring gaseous pollutants. When the gaseous pollutants were included in the analyses, the estimated associations between PM10 and mortality remained, though they were somewhat reduced. These results suggest that the effects are likely due to the particulate exposures; they cannot readily be explained by coexisting weather stresses or other pollutants.

An expansion of the NMMAPS study to 90 U.S. cities also reported association with PM10 levels and mortality (Samet et al. 2000b; Health Effects Institute 2003). It was discovered that this study was one that used a software package with inappropriate default settings. The investigators have reanalyzed the data using corrected settings for the software (Dominici et al. 2002; Health Effects Institute 2003). When the estimates for the 90 cities in the study were recalculated, the estimate changed from 0.41% increase in mortality for a 10 μg/m^3 increase in PM10 to a 0.27% increase. There remained a strong positive association between acute exposure to PM10 and mortality. When an alternate model was used, the average estimate was 0.21% increase in mortality per 10 μg/m3 increase in PM10 (Health Effects Institute 2003). Thus while the quantitative estimate was reduced, the major findings of the study did not change.

Studies of short-term exposures to PM2.5 have also found associations with increases in mortality. The NMMAPS study conducted a national analysis of PM2.5 mortality association for 1999-2000. The risk estimates were 0.29% for all-cause mortality and 0.38% for cardio-respiratory mortality (Dominici et al. 2007). In its 2009 review, U.S. EPA determined that estimates for PM2.5 generally are in the range of 0.29 to 1.21% increase in total deaths per 10 μg/m^3 increase in 24-hour PM2.5 levels. The estimates for cardiovascular related mortality range from 0.03 to 1.03% per 10 μg/m^3, and for respiratory mortality estimates range from 1.01 to 2.2% per 10 μg/m^3 24-hour PM2.5 (U.S. EPA 2009). Figure I-4 shows a summary of recent studies of mortality and short-term PM2.5 exposures.

Several studies have attempted to assess the relative importance of particles smaller than 2.5 μm and those between 2.5 μm and 10 μm (PM10-2.5). While some studies report that PM2.5 levels are better predictors of mortality effects, others suggest that PM10-2.5 is also important. Most of the studies found higher mortality associated with PM2.5 levels than with PM10-2.5. For example, a study of six cities in the U.S. found

that particulate matter less than 2.5 µm was associated with increased mortality, but that the larger particles were not. In the U.S. EPA review (U.S. EPA 2009), several studies were presented that that found associations of PM10-2.5 and mortality. Some of the studies showed differences by region of the U.S. In one study of 47 U.S. cities that had both PM2.5 and PM10 data available to calculate PM10-2.5 as a difference, overall, the study found a significant association between the computed PM10-2.5 and all-cause, cardiovascular, and respiratory mortality. The study also reported differences by season and climate area (Zanobetti et al. 2009).

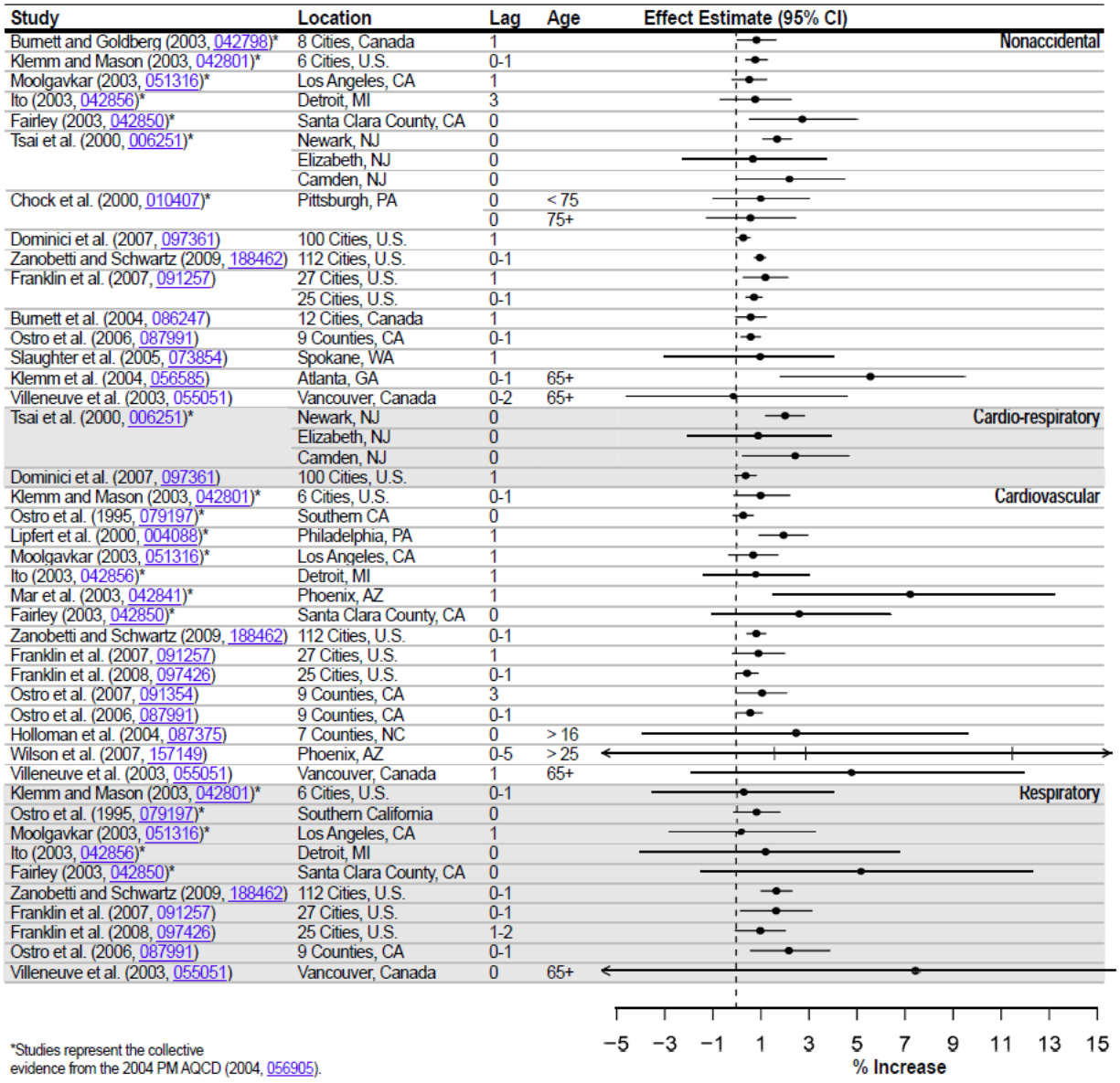


FIGURE I-4

Summary of Nonaccidental Mortality per 10 µg/m3 Increase in PM2.5 Short-term Exposures

(from (U.S. EPA 2009), Figure 6-27). "Lag" indicates the number of days between the exposure and the outcome assessed.

The relative importance of both PM2.5 and PM10-2.5 may vary in different regions depending on the relative concentrations and components, which can also vary by season. A major knowledge gap is the relative paucity of direct measurements of PM2.5-10. Most estimates are made by subtracting PM2.5 from PM10 measured at co-located samplers, a process that is subject to errors that are inherent in the subtracting of one relatively large number from another. More research is needed to better assess the relative effects of coarse (PM10-2.5) fractions of particulate matter on mortality. A graph from the U.S. EPA review is included in the figure below to demonstrate ranges of mortality findings associated with coarse particulates.

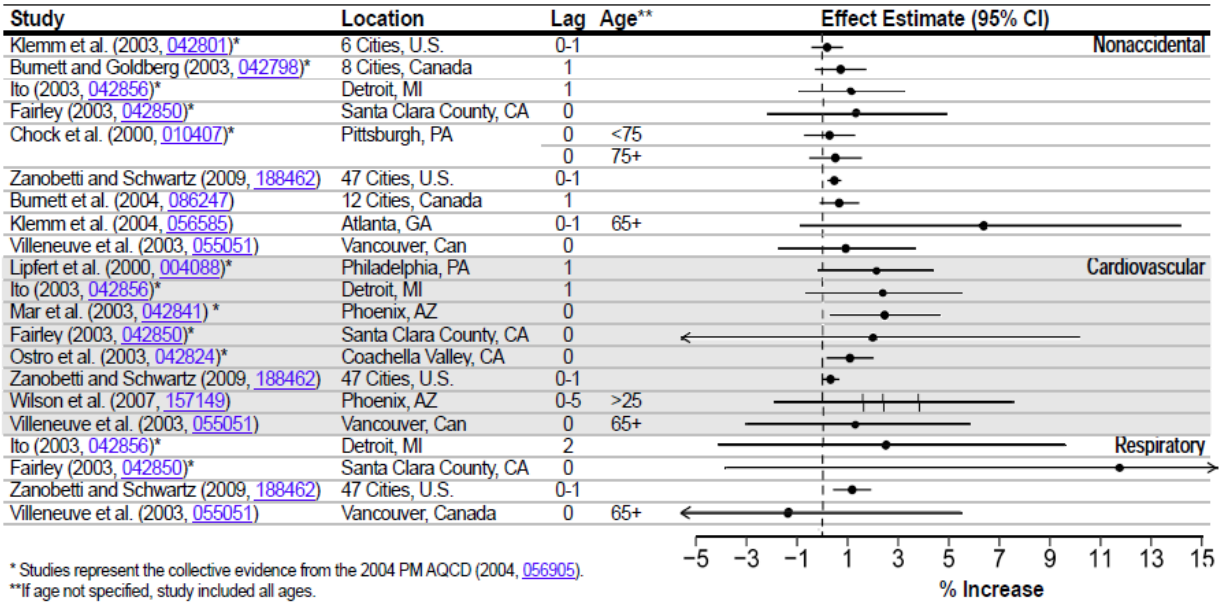


FIGURE I-5

Summary of Percent Increase in Total (Nonaccidental) and Cause-Specific Mortality Per 10 µg/m3 Increase in PM10-2.5 (from (U.S. EPA 2009), Figure 6-30). "Lag" indicates the number of days between the exposure and the outcome assessed.

A number of studies have evaluated the association between particulate matter exposure and indices of morbidity such as hospital admissions, emergency room visits or physician office visits for respiratory and cardiovascular diseases. The effect estimates are generally higher than the estimates for mortality. The effects are associated with measures of both PM10 and PM2.5. Effects are also associated with PM10-2.5.

In the NMMAPS study, hospital admissions for those 65 years or older were assessed in 14 U.S. cities. Several models were compared to estimate associations of hospital admissions for specific disease categories and short-term PM10 levels. Hospital admissions showed an increase ranging from 0.68 – 1.47% for cardiovascular diseases, a range of 1.46 – 2.88% increase for COPD, and a range of 1.31 – 2.86% increase for pneumonia per 10 $\mu g/m^3$ increase in PM_{10} (Samet et al. 2000b). In the reanalysis of the study (Health Effects Institute 2003), it was found that when using different models, the pollution coefficients were generally lower. However, the authors note that most of the conclusions of associations with PM10 exposures and hospital admissions held. Two recent Southern California studies evaluated associations between short-term PM2.5 levels and asthma-related hospital or emergency admissions. One study, based in Orange County, reported increased risk of asthma-related hospital encounters with increased ozone and PM2.5 in the warm seasons, and with CO, NOx, and PM2.5 in the cool seasons (Delfino et al. 2014). The second study, conducted in Los Angeles County, reported monthly average PM2.5, CO, and NO_2 levels were positively associated with asthma hospitalization rates (Delamater et al. 2012).

Similarly, school absences, lost workdays, and restricted activity days have also been used in some studies as indirect indicators of acute respiratory conditions (Ostro 1987; Ostro 1990; Ransom et al. 1992; Gilliland et al. 2001; Park et al. 2002; Hales et al. 2016). These observations help support the hypotheses that particulate matter exposures increase inflammation in the respiratory tissues and may also increase susceptibility to infection (U.S. EPA 2009).

Some studies have reported that short-term particulate matter exposure is associated with changes in lung function (lung capacity and breathing volume); upper respiratory symptoms (hoarseness and sore throat); and lower respiratory symptoms (increased sputum, chest pain and wheeze). The severity of these effects is widely varied and is dependent on the population studied, such as adults or children with and without asthma. Sensitive individuals, such as those with asthma or pre-existing respiratory disease, may have increased or aggravated symptoms associated with short-term particulate matter exposures. Several studies have followed the number of medical visits associated with pollutant exposures. A range of increases from 1 to 4% for medical visits for respiratory illnesses was found corresponding to a 10 $\mu g/m^3$ change in PM10. A number of studies also looked at levels of PM2.5 or PM10-2.5. The findings suggest that both the fine and coarse fractions may have associations with some respiratory symptoms (U.S. EPA 2009). Among the newer health endpoints

evaluated in recent studies of short-term effects of PM2.5 is stroke. One recent meta-analysis evaluated 16 studies of short-term PM2.5 exposures and estimated a 5% increased risk of stroke for each 10 $\mu g/m^3$ increase in PM2.5 (Shin et al. 2014).

The biological mechanisms by which particulate matter can produce health effects have been investigated in laboratory studies. Brook et al. (Brook et al. 2010) summarized three likely pathways by which PM exerts it effects on cardiovascular health outcomes: (1) PM can activate inflammatory pathways and cause systemic oxidative stress, leading to the production of pro-inflammatory cytokines; (2) PM can disrupt the autonomic nervous system leading to increased blood pressure, increased arrhythmic potential, and decreased heart rate variability; and (3) PM, particularly UFPs or particle constituents such as organic compounds and metals, can enter the bloodstream and cause increased constriction of the blood vessels and increased blood pressure. Each of these pathways may also lead to the formation of reactive oxygenated species (ROS, or free radicals) that can cause DNA oxidation and systemic inflammation. Inflammatory responses in the respiratory system in humans and animals can lead to inflammation in fat tissues and in the liver, which can lead to vascular dysfunction (e.g. atherosclerosis), changes in metabolic function (e.g. insulin resistance), and increased thrombotic potential (Brook et al. 2010). Several reviews discuss mechanistic studies in detail (Brunekreef et al. 2002; Brook et al. 2004; Brook et al. 2010).

Some studies have examined the health effects of short-term exposures to specific PM constituents and sources (Lippmann 2014; Basagana et al. 2015; Atkinson et al. 2016). While there is some evidence suggesting possible links with specific constituents or sources, such as diesel exhaust, sulfates (related to coal combustion), and certain metals, the U.S. EPA determined that there were not enough studies evaluating short-term constituent- or source-specific exposures at the time of the previous Integrated Science Assessment to be able to make a causal determination (U.S. EPA 2009).

Long-Term Exposure Effects of PM

Numerous studies have evaluated the health effects of long-term (months to years) or chronic exposure to particulate matter, with the largest number of studies examining cardiovascular and respiratory health endpoints, as well as mortality. Other health outcomes that have been linked to long-term PM exposures include reproductive effects, cancer outcomes, and, more recently, metabolic syndromes and neurological effects. The U.S. EPA 2009 Integrated Science Assessment for Particulate Matter (ISA

for PM) concluded that sufficient evidence is available to support a causal determination for long-term PM2.5 exposures and cardiovascular and mortality effects, and a likely causal relationship for respiratory effects. A summary of the evidence is presented below, focusing on the long-term effects of PM2.5 exposures.

Long-Term Particulate Matter Exposures and Mortality

Since the initial promulgation by U.S. EPA of the National Ambient Air Quality Standards for PM2.5, controversy has remained over the association of mortality and exposures to PM2.5. Several large, prospective cohort studies conducted in the U.S. and Canada were used to evaluate long-term PM exposures and mortality, including total number of deaths and deaths due to specific causes. The strongest and most consistent evidence of long-term PM2.5 effects are for cardiovascular mortality, particularly ischemic heart disease, and there is evidence that ambient PM2.5 exposure is associated with and lung cancer mortality (Dominici et al. 2006; Krewski et al. 2009; Jerrett et al. 2013; International Agency for Research on Cancer 2015). Below is a brief discussion of the evidence linking PM and mortality reviewed in the U.S. EPA 2009 ISA along with more recently published studies, with a focus on large prospective studies and studies conducted in California or Southern California.

In the assessment of evidence for mortality outcomes linked to long-term PM exposures, the 2009 U.S. EPA ISA for PM reviewed 15 studies evaluating PM2.5 exposures, 2 studies evaluating PM10-2.5 exposures, and 5 studies evaluating PM10 exposure. The majority of these studies were conducted in the United States, and 3 of the studies of PM2.5 exposures were conducted in California or Southern California. Previous reviews conducted in 1996 and 2004 by U.S. EPA assessed evidence primarily from large prospective cohort studies, such as the Harvard Six Cities Study (Dockery et al. 1993), the American Cancer Society (ACS) Study (Pope et al. 1995; Pope et al. 2002), and the Seventh-Day Adventist Health Air Pollution (AHSMOG) Study (Abbey et al. 1999; McDonnell et al. 2000). The U.S. EPA 2004 PM Air Quality Criteria Document concluded that there was strong evidence linking long-term PM2.5 exposures to all-cause and cardiopulmonary mortality, but not enough evidence for a link with PM10-2.5. The 2009 U.S. EPA ISA for PM similarly concluded that the newer studies provide additional evidence to support a causal determination for long-term PM2.5 exposures and increased mortality risk, but there continues to be insufficient evidence supporting such a link with particles in the coarse fraction. This most recent U.S. EPA review evaluated the additional updated analyses of the previously-established large cohort studies (Harvard Six Cities, ACS, AHSMOG, and

Veterans studies), and noted two new major cohorts that provide further evidence linking PM2.5 and mortality: the Women's Health Initiative (WHI) study (Miller et al. 2007) and the Medicare Cohort Studies (Eftim et al. 2008).

The American Cancer Society Cancer Prevention Study II (ACS) is a large, prospective national cohort study of over one million participants in the U.S. recruited from all 50 states, the District of Columbia and Puerto Rico, and followed over many years. Over the past two decades, studies using data from this cohort have reported associations for PM2.5 for both total mortality and cardiorespiratory mortality (Pope et al. 1995; Krewski 2000; Pope et al. 2002; Jerrett et al. 2005; Krewski et al. 2009; Jerrett et al. 2013; Pope et al. 2015). The original study reported that long-term exposures to fine particulate air pollution were associated with cardiopulmonary and lung cancer mortality (Pope et al. 1995). In a reanalysis of the data (Krewski 2000), mortality rates and PM2.5 levels were analyzed for 50 metropolitan areas of the U.S. Average (median) levels from monitors in each metropolitan area were used to estimate PM2.5 exposures. At these levels of aggregation, regional differences in the association of PM2.5 and mortality were noted, with higher mortality risks in the Northeast and Midwest, and more moderate mortality risks in the West.

Another follow-up study of the American Cancer Society cohort confirmed and extended the findings in the initial study. The researchers estimated that, on average, a 10 µg/m3 increase in fine particulates was associated with approximately a 4% increase in total mortality, a 6% increase in cardiopulmonary mortality, and an 8% increase in risk of lung cancer mortality (Pope et al. 2002). In an additional reanalysis and extension of the American Cancer Society cohort from 1982 to 2000 (Krewski et al. 2009), and including additional metropolitan areas for the most recent years, effects estimates on mortality were similar, though somewhat higher than those reported previously. The extended analyses included an additional 11 years of cohort follow-up compared to the original study. The authors reported positive and significant association between a 10 $\mu g/m^3$ change in PM2.5 level and all-cause, cardiopulmonary disease, and ischemic heart disease deaths. Mortality from ischemic heart disease was associated with the largest risk estimates.

Subsets of the ACS study data have also been evaluated to estimate effects in California and the metropolitan Los Angeles area (Jerrett et al. 2005; Jerrett et al. 2013). These results are discussed further below, along with results of other California or Southern California-based studies.

The Harvard Six Cities Study evaluated several size ranges of particulate matter and reported significant associations with particulate matter ≤15 μm in aerodynamic diameter (PM15), PM2.5, sulfates, and non-sulfate particles, but not with coarse particles (defined in this study as PM15-2.5). An extension of the Harvard Six Cities Cohort confirmed the association of mortality with PM2.5 levels (Laden et al. 2006). These studies provide evidence that the fine particles, as measured by PM2.5, may be more strongly associated with mortality effects from long-term particulate matter exposures than are coarse particles. An update to this study covering a follow-up over the years 1974 to 2009 was recently published (Lepeule et al. 2012). Findings indicated a linear relationship of PM2.5 levels and mortality from all causes, cardiovascular causes, and from lung cancer. According to the authors, the PM2.5 levels decreased over time, but no evidence of a threshold for these effects was found.

AHSMOG is a cohort study of non-Hispanic white Seventh-day Adventists in California, with participants followed starting from the late 1970's. Confounding due to smoking in this study is unlikely due to very low smoking rates in this population; however, the study is limited in its the ability to apply the findings to other population groups. The study has linked long-term PM10 exposures and other air pollutants to deaths from all natural causes and deaths due to lung cancer among males (Abbey et al. 1999), although the authors concluded that these associations were likely due to exposures to fine particles rather than the coarse fraction of PM10 (McDonnell et al. 2000). In a re-analysis of the data, the study found PM2.5 was associated with an increased risk of coronary heart disease mortality among females but not among males (Chen et al. 2005). Similar associations among females only were found for coarse particles and PM10.

Other cohort studies include an analysis of mortality and PM2.5 exposures in a Medicare enrollee population. Zeger et al. (Zeger et al. 2008) assembled a Medicare enrollee cohort by including all Medicare enrollees residing in over 4,500 zip codes with centroids within six miles of a PM2.5 monitor. PM2.5 data was obtained from the monitoring stations, and mean annual levels were calculated for the zip codes within six miles of each monitor. The authors found that long-term exposures to PM2.5 was associated with all-cause mortality for the eastern and central portions of the U.S., and these mortality risk estimates were similar to those previously published in the Six Cities Study and the American Cancer Society cohorts. The authors reported that there were no statistically significant associations between zip code levels of PM2.5 and all-cause mortality rates in the western region of the U.S. This finding was attributed largely to the higher PM2.5 levels in Los Angeles area counties compared

to other western urban areas, but there were not higher mortality rates in the Los Angeles area counties. Several factors could explain this finding. The authors note that the toxicity of the PM mixture may differ by location, e.g. with higher PM2.5 sulfate levels in the eastern region. In addition, the use of ecological data rather than individual-level data for exposure assessment and some confounding factors, and the assessment of all-cause mortality rather than cause-specific mortality may have impacted the results of this study. The authors further reported that they found no associations of PM2.5 with all-cause mortality in persons aged 85 years or higher, which may reflect other competing causes of death in this age group not related to air pollution exposures.

The Women's Health Initiative (WHI) Study is a nationwide cohort of post-menopausal women in 36 metropolitan areas of the U.S. who had no history of cardiovascular disease (Miller et al. 2007). The study found that long-term exposure to PM2.5 was associated with a 24% increased risk of cardiovascular disease and a 76% increased risk of death from cardiovascular causes for each additional 10 $\mu g/m^3$ of PM2.5; these relative risk estimates are larger than those reported in the ACS and Six Cities Studies, but differences in health status, PM composition, and overall mortality risk in these distinct populations may account for such differences in the effect estimates. Another large cohort study focusing on women is the Nurses' Health Study, which found that PM10 exposures were associated with all-cause mortality and fatal coronary heart disease, with exposures 24 months prior to death having the strongest effects (Puett et al. 2008).

A recent pooled analysis of 22 European cohorts and including over 350,000 participants evaluated long-term air pollution exposures and exposure to PM2.5, PM10, and nitrogen oxides, using land use regression models to estimate exposures (Beelen et al. 2014). The authors reported that a 5 $\mu g/m^3$ increase in PM2.5 was associated with approximately a 7% increase in mortality from natural causes.

Examples of studies estimating mortality risks and PM2.5 levels are shown in the figure below.

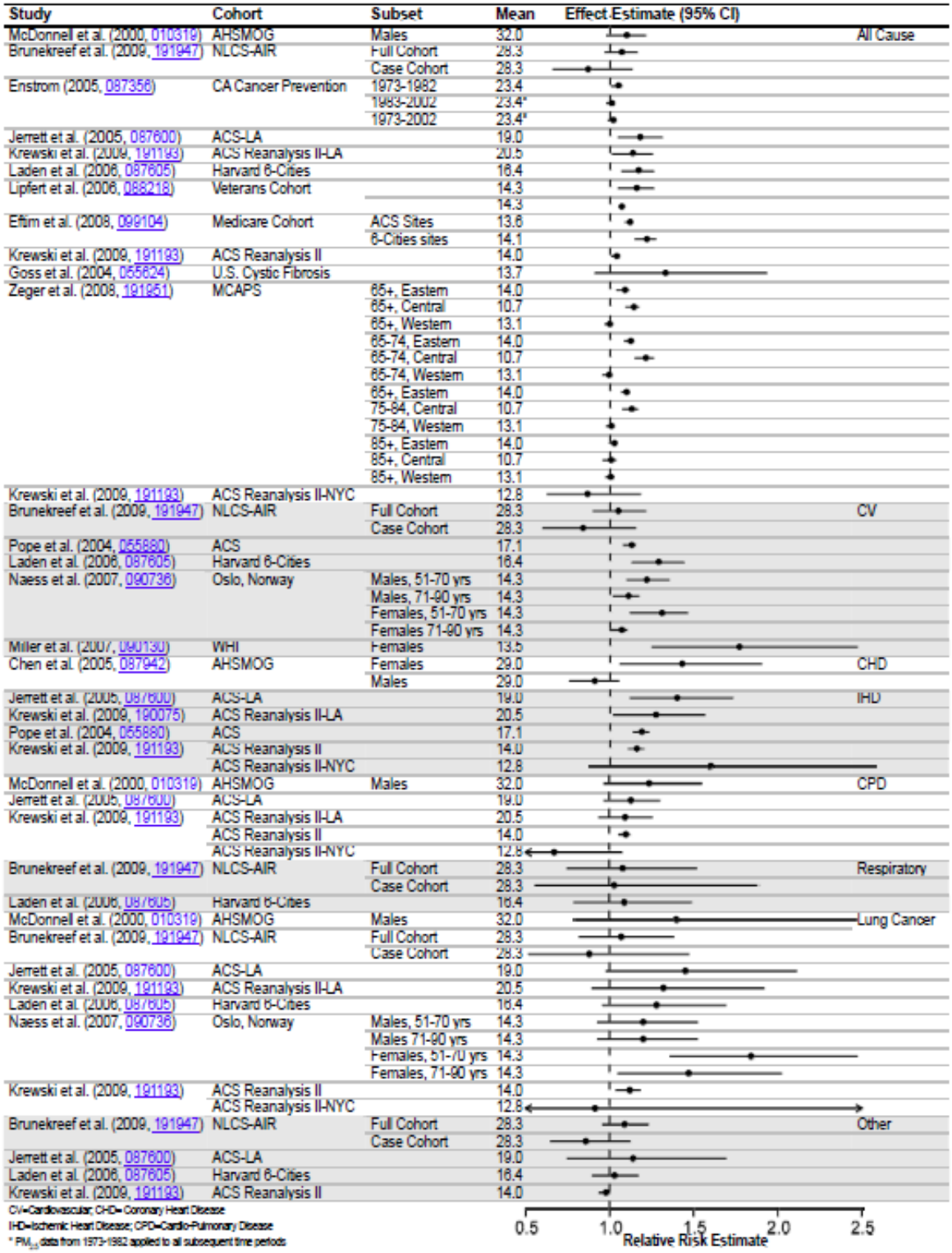


FIGURE I-6

Mortality Risk Estimates, Long-Term Exposure to PM2.5 in Cohort Studies (From (U.S. EPA 2009), Figure 7-7). "Mean"=mean PM2.5 exposure estimates in the study.

In addition to the AHSMOG study, other analyses of mortality and PM2.5 levels specific to California have also been reported, including an analysis of a subset of the ACS II data. An analysis of the ACS II study (Jerrett et al. 2013) followed individuals in California from that cohort recruited starting in 1982, with follow-up to 2000. PM2.5 levels at subject residences were estimated using land use regression models. The authors noted that mortality rates differ in urban areas compared to non-urban areas, and so included a variable for this in the model to estimate pollution effects on mortality. All-cause mortality, mortality from cardiovascular disease, and mortality from ischemic heart disease were positively associated with PM2.5 levels in single-pollutant models. These associations with PM2.5 remained after additional adjustment for ozone levels. Because of moderate correlations across pollutants, it may not be possible to draw conclusions about which pollutant(s) in this mixture cause the observed effects. Positive associations of all-cause and certain cause-specific mortality rates with estimated NO_2 and ozone levels were also found. The authors concluded that these results indicate that several components of combustion-related pollutant mixture are associated with mortality.

A study analyzed data from the California Teachers Study cohort of over 100,000 active and retired school teachers recruited in 1995, and followed through 2005 (Lipsett et al. 2011). Pollutant exposures at the subject residences were estimated using data from ambient monitors, and extrapolated using a distance weighted method. The authors reported that a 10 $\mu g/m^3$ increase in PM2.5 was associated with a 20% risk increase in mortality from ischemic heart disease, but no associations were found with all-cause, cardiovascular, or lung cancer mortality.

A more recent analysis of the California Teachers Study cohort from 2001 through 2007 estimated the association between particulate pollutants and all-cause, cardiovascular, ischemic heart disease, and respiratory mortality (Ostro et al. 2015). Exposure data at the residential level were estimated by a chemical transport model that computed pollutant concentrations from over 900 sources in California. Besides particle mass, monthly concentrations of 11 species and 8 sources or primary particles were generated at 4-km grids. The results were reported as finding statistically significant associations of ischemic heart disease mortality with PM2.5 mass and several of its components (Figure I-7). The study also found significant positive associations between ischemic heart disease mortality and ultrafine particle mass as well as several ultrafine particulate components including elemental carbon, organic carbon, copper, metals, meat cooking, and mobile source derived components. An earlier study using data from the same cohort had used monitoring data to estimate

mortality risk, and similarly reported increased risk of all-cause, cardiopulmonary, and ischemic heart disease mortality with higher exposures to PM2.5 mass. This study also reported increased ischemic heart disease risk with higher exposures to PM2.5 constituents such as organic carbon, sulfates, and nitrates (Ostro et al. 2010).

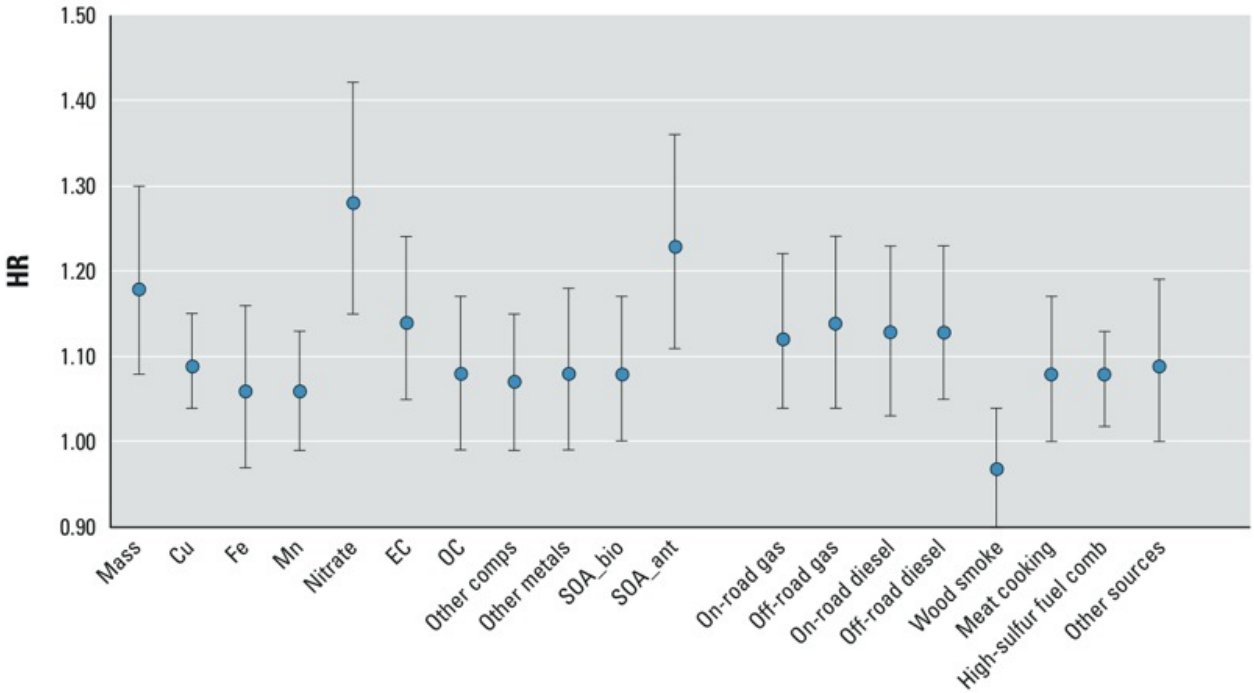


FIGURE I-7

Association of PM2.5 constituents and sources with Ischemic Heart Disease mortality (Hazard Ratios and 95% Confidence Intervals) using interquartile range. Abbreviations: comb = combustion; comps = components; SOA_bio= secondary organic aerosols from biogenic sources (derived from long-chain alkanes, xylenes, toluenes, and benzene and their oligomers); SOA_ant=secondary organic aerosols from biogenic sources (derived from isoprenes, monoterpenes, and sesiquiterpenes and their oligomers). (From (Ostro et al. 2015))

A cohort of elderly individuals (average age of 65 years in 1973) recruited from 11 California counties was followed over several years (Enstrom 2005). A positive association for long-term PM2.5 exposure with all-cause deaths was reported from 1973–1982. However, no significant association was found in the later time period of 1983–2002. PM2.5 levels were obtained from measurements made during 1979- 1983 by the EPA as part of the Inhalable Particle Monitoring Network and the cohort was confined to those participants in the American Cancer Society Cancer Prevention Study I who were living in the 11 counties that had one of the monitors. Pollutant levels

were estimated using data from these monitors and averaged over each county, which may lead to exposure misclassification and bias toward finding no effect.

The California Air Resources Board recently conducted a cross-sectional study of long-term PM2.5 exposures in rural and urban areas within California, using ambient monitoring data from 116 stations in the monitoring network, and calculating zip code-level exposure estimates (Garcia et al. 2016). The study observed larger effect sizes for increased PM2.5-related mortality risk in rural compared to urban areas from all causes, cardiovascular disease and cardiopulmonary disease. In urban areas, the study found PM2.5 exposures to be associated with increased risk of cardiovascular disease, ischemic heart disease, and cardiopulmonary disease; however, for all-cause non-accidental mortality risk, only an exposure model restricted to people living within 10 km of a monitoring station in urban areas showed an association with PM2.5. This study did not control for the potential confounding effects of smoking.

A recent study analyzed data from the National Institutes of Health AARP Diet and Health cohort, including about 160,000 participants in California (Thurston et al. 2016). Census tract-level PM2.5 exposures were estimated based on land use regression models. For the California cohort, PM2.5 levels were associated with an approximately 10% increase in cardiovascular disease mortality risk for each additional 10 $\mu g/m^3$ of PM2.5. A small but positive effect estimate was found for all-cause mortality in California, and no association was found for respiratory mortality in the California cohort, although the estimates indicated uncertainty in the magnitude and direction of these effects.

A few studies have focused on particulate matter exposure and health effects in residents of Southern California. Two analyses of the American Cancer Society II cohort, for example, focused specifically on the Los Angeles Metropolitan area using methods to estimate exposures on a finer geographical scale than previous studies that used geographic scales at the county or metropolitan area. Improved exposure estimation methods reduce potential bias from exposure misclassification. Using data from monitoring stations in the Los Angeles area, one study applied interpolation methods (Jerrett et al. 2005) and another applied land use regression techniques (Krewski et al. 2009) to estimate PM2.5 exposures to the study participants. Significant associations of PM2.5 with mortality from all causes and cardiopulmonary disease were reported, with the magnitude of risks being higher than those from the national studies of the American Cancer Society II cohort. Such improved exposure estimation techniques can reduce misclassification bias in epidemiological studies. It

should be noted that various analyses were presented in these as well as other studies to estimate the influence of various individual-level and ecologic variables that might also be related to health effects risks. Including such variables helps control for potential confounding, but generally reduces the estimated association between PM2.5 and all-cause mortality. It may be illustrative to describe some of the estimates from the various calculations as presented by the authors of the Los Angeles area cohort (Krewski et al. 2009). In the descriptions in Table I-8, HR refers to the "hazard ratio" expressed for a 10 μg/m^3 change in PM2.5 exposure, followed by the 95% Confidence Interval. For example, if the hazard ratio is 2, the risk would be twice as high; and, conversely if the hazard ratio is 0.5, the risk would be one-half of that of the reference group. Several of the analyses results follow as excerpted from Krewski, 2009. Table I-8 includes PM2.5, plus various additional individual and ecological variables. Similar effects of covariate adjustment were seen for hazard ratios for mortality from ischemic heart disease, although effect estimates were stronger for ischemic heart disease mortality compared to those for all-cause mortality.

TABLE I-8

Influence of Adding Confounding Variables on All-Cause Mortality

VARIABLE INCLUDED	HAZARD RATIO per 10 μg/m^3 change in PM2.5 exposure
PM2.5 alone (stratified for age, sex, and race)	1.197 (95% CI, 1.082–1.325);
PM2.5 with 44 individual-level covariates	1.143 (95% CI, 1.033–1.266)
PM2.5 with 44 individual-level covariates and the ecologic covariate of unemployment	1.127 (95% CI, 1.015–1.252)
PM2.5 with 44 individual-level covariates and social factors extracted from the principal component analysis (which account for 81% of the total variance in the social variables)	1.142 (95% CI, 1.026–1.272).
PM2.5 with 44 individual-level covariates and all ecologic covariates that were individually associated with mortality in bivariate models with PM2.5 exposure	1.115 (95% CI, 1.003–1.239)
PM2.5 parsimonious model that included 44 individual-level covariates and ecologic confounder variables that both reduced the pollution coefficient and had associations with mortality	1.126 (95% CI, 1.014–1.251)

(From Krewski, 2009)

U.S. EPA also released a Regulatory Impact Analysis (U.S. EPA 2012) which looked at the costs and benefits of alternate PM2.5 standard levels. As part of the analysis, U.S. EPA looked at California-specific studies regarding PM2.5 and mortality published in the scientific literature. The U.S. EPA analysis concluded "most of the cohort studies conducted in California report central effect estimates similar to the (nation-wide) all-cause mortality risk estimate we applied from Krewski et al. (2009) and Laden et al. (2006) albeit with wider confidence intervals. A couple of cohort studies conducted in California indicate higher risks than the risk estimates we applied." Thus, in U.S. EPA's judgment, the California-related studies provided estimates of mortality consistent with or higher than those from the national studies.

Long-Term Particulate Matter Exposures and Cardiovascular Effects

Studies of cardiovascular mortality provide the strongest evidence of an association between PM2.5 exposures and cardiovascular effects. The U.S. EPA 2009 ISA review determined that the evidence is sufficient to infer a causal relationship between long-term PM2.5 exposures and cardiovascular effects. In addition to the studies of mortality, other epidemiological studies provide additional evidence of sub-clinical and clinical cardiovascular effects, while toxicological studies suggest a plausible biological mechanism for such effects (Fanning et al. 2009; U.S. EPA 2009).

Epidemiological studies of subclinical effects typically have used subclinical measures of atherosclerosis, which is an underlying disease contributing to many clinical cardiovascular outcomes such as myocardial infarction, sudden cardiac death, stroke, and vascular aneurysms (U.S. EPA 2009). A study in Southern California residents used the carotid intima-media thickness (CIMT) as a measure of subclinical atherosclerosis (Kunzli et al. 2005). The subjects' residential areas were geocoded and a geospatial extrapolation of ambient monitoring data was used to assign annual mean concentrations of ambient PM2.5. The authors report results of an association between atherosclerosis and ambient air pollution as measured by PM2.5. The associations of PM2.5 and CIMT were strongest in women ≥ 60 years of age. The Multi-Ethnic Study of Atherosclerosis (MESA) is a population-based study of people living in 6 U.S. cities or counties, including Los Angeles, CA (Diez Roux et al. 2008). The MESA study reported that 20-year average PM2.5 exposures corresponded to a small increase in CIMT, although the magnitude of the increase was much smaller than the Kunzli 2005 study. Such differences may be attributable to differences in the study populations.

Other sub-clinical outcome measures for atherosclerosis in the MESA study were weakly associated or not associated with PM exposures.

Clinical cardiovascular outcomes have also been examined in several epidemiological studies, including two that were based on prospective cohort studies: the Women's Health Initiative (WHI) Observational Study (Miller et al. 2007) and the Nurses' Health Study (Puett et al. 2008). Both these studies also examined cardiovascular mortality, and found links with long-term particulate matter exposures. The WHI study included only women who were free of cardiovascular disease at enrollment, and estimated PM2.5 exposures using a nearest monitor approach. The study found PM2.5 exposures to be associated with cardiovascular disease outcomes, including myocardial infarction, revascularization, stroke, coronary heart disease death, and cerebrovascular disease (Miller et al. 2007). An analysis of the Nurses' Health Study included women without a history of myocardial infarction and who lived in certain metropolitan areas in the northeastern U.S. (Puett et al. 2008). Long-term PM10 exposures were estimated using land use regression models as well as air pollution monitoring data. This study found positive associations with the risk of all-cause and coronary heart disease mortality, and the results were suggestive of a link to coronary heart disease events although there was a great deal of uncertainty in this result. Other studies conducted in the U.S. and Europe have examined clinical cardiovascular outcomes with varying results (U.S. EPA 2009).

The U.S. EPA 2009 ISA concluded that epidemiologic studies, along with toxicological evidence linking PM exposures to atherosclerosis and other cardiovascular outcomes, provides evidence linking PM to cardiovascular effects and mortality. While the associations between PM and subclinical and clinical measures have inconsistent results, the consistency of the studies linking PM exposures to cardiovascular mortality and the coherence of the toxicological studies provide support for U.S. EPA's causal determination.

Long-Term Particulate Matter Exposures and Respiratory Effects

The U.S. EPA 2009 ISA review determined that the evidence for long-term particulate matter exposures on respiratory effects is likely to be causal. Several studies, including prospective cohort studies, have assessed the effects of long-term particulate matter exposure on respiratory symptoms and lung function changes. Consistent, positive associations have been found with respiratory symptoms such as bronchitis and decreased lung function in children.

The Southern California Children's Health Study established cohorts of school children from 12 Southern California communities, and followed these participants over time. One of the early studies from this cohort reported positive associations of particulate matter with prevalent bronchitis or phlegm among children with asthma. These effects were also associated with NO_2 and acid vapor levels (McConnell et al. 1999). Another study based on this cohort reported a lower rate of growth in lung function in children living in areas with higher levels of particulate pollution (Gauderman et al. 2000). Decreases in lung function growth were associated with PM10, PM2.5, PM10-2.5, acid vapor, and NO_2. There was no association with ozone levels. The investigators were not able to identify independent effects of the pollutants but noted that motor vehicle emissions are a major source of the pollutants.

A follow-up study on a second cohort of children confirmed the findings that decreased lung function growth was associated with particulates, nitric oxides, and elemental carbon levels (Gauderman et al. 2002). Elemental carbon is often used as a measure for diesel particulate. Additionally, children who moved to areas with less air pollution were found to show improvement in lung function growth rate (Avol et al. 2001). By the time the fourth graders graduated from high school, a significant number showed lower lung function. The risk of lower lung function was about five times higher in children with the highest PM2.5 exposure when compared to the lowest exposure communities (Gauderman et al. 2004).

A follow-up report from the Children's Health Study assessed whether improving air quality in Southern California over the past decade has led to beneficial changes in health (Gauderman et al. 2015). It was reported that as the levels of nitrogen oxide and fine particulates were reduced as the result of reductions in air pollution emissions, the deficits in lung function growth were also of a smaller magnitude. Recently, the Children's Health Study cohort data were also used to evaluate associations with bronchitic symptoms in children (Berhane et al. 2016). The study found that reductions in NOx, ozone, and PM10 and PM2.5 were associated with decreases in bronchitic symptoms, with stronger effects observed in children with asthma. These results indicate that improvements in air quality, as measured by fine particulate and nitrogen oxides, are associated with improvements in children's health in Southern California.

A limited number of studies have linked PM exposures to asthma incidence. In an analysis of the Children's Health Study in Southern California, Islam et al. found that while children with better lung function are generally at lower risk of developing asthma, living in an area with high PM2.5 levels offset this protective characteristic; in other words, this study related high PM2.5 levels with new onset asthma in children

(Islam et al. 2007). The U.S. EPA 2009 ISA report also reviewed two European studies that linked PM2.5 with asthma onset in children (Brauer et al. 2007) and adults (Kunzli et al. 2009). Two recent studies were identified in our literature search: the first study used the Sister Study national cohort and found that a 3.6 $\mu g/m^3$ increase in PM2.5 was associated with a 20% increased risk of incident asthma and a 14% increase in incident wheeze among adult females (Young et al. 2014); the second study was a study of Medicaid-enrolled children in Harris County, Texas, and found PM2.5 was associated with new-onset asthma in single-pollutant models (Wendt et al. 2014). However, accounting for the potential effects of other pollutants added substantial uncertainty in the overall effect estimates for PM2.5, meaning that it is difficult to distinguish in this study whether the effects are due to PM2.5 or other pollutant exposures.

The U.S. EPA 2009 ISA also noted that studies from many different locations, including Mexico City, Sweden, and a national cohort in the U.S. provide additional coherent and consistent evidence of respiratory effects associated with PM exposures.

Long-Term Particulate Matter Exposures and Cancer

The U.S. EPA 2009 ISA review concluded that existing evidence is suggestive of a link between PM2.5 and cancer, with studies of lung cancer providing the strongest evidence. Additionally, the International Agency for Research on Cancer (IARC) recently designated outdoor air pollution and particulate matter as carcinogenic to humans (Group 1 carcinogens), and a meta-analysis provided quantitative evidence for the associations between particulate matter and lung cancer risk (Hamra et al. 2014; International Agency for Research on Cancer 2015). The IARC review included studies evaluating associations between outdoor air pollution and lung cancer, urinary bladder cancer, breast cancer, leukemia and lymphoma, childhood cancers, and total cancers. Among these cancers, the IARC Working Group concluded that outdoor air pollution and particulate matter cause lung cancer, and that positive associations were observed between outdoor air pollution and urinary bladder cancer. The IARC Working Group also noted that associations with childhood leukemia were suggestive of an association, and, while there were some inconsistencies across studies, an association could not be ruled out. To estimate overall lung cancer risk, the meta-analysis included 14 studies reporting on PM2.5 and 9 studies reporting on PM10; the vast majority of these were cohort studies from North America and Europe. The meta-analysis found positive associations for both PM10 and PM2.5 and lung cancer risk, with the PM2.5 results being more consistent.

Long-Term Particulate Matter Exposures and Reproductive Health Outcomes

Studies from the U.S., Brazil, Mexico, the Czech Republic, South Korea, Japan, and Taiwan have reported that neonatal and early postnatal exposure to particulate matter may lead to increased infant mortality (U.S. EPA 2009). One of these studies was conducted in Southern California, and found increased risks for deaths among infants between one and 12 months old associated with exposures to particulates and other pollutants; however, no effect was seen for neonatal mortality (defined as mortality in the first month after birth) (Ritz et al. 2006).

Numerous other studies report evidence indicating that particulate matter exposure during pregnancy may be associated with adverse birth outcomes, with relatively consistent evidence linking PM2.5 and PM10 exposures to low birth weight or decreases in birth weight (Bobak et al. 1999; Sram et al. 2005; Stieb et al. 2012). Among the studies reviewed in the 2009 U.S. EPA ISA for particulate matter or in our literature search for more recent and/or local studies, several studies of low birth weight (defined as <2,500g or approximately 5.5 pounds at birth) or reductions in birth weight were conducted in California or in the Southern California region (Basu et al. 2004; Parker et al. 2005; Salam et al. 2005; Wilhelm et al. 2005; Morello-Frosch et al. 2010; Wilhelm et al. 2012; Basu et al. 2014; Laurent et al. 2014). Two of these studies were conducted in Southern California (both in Los Angeles County) and were published since the last AQMP in 2012, and both examined low birth weight among full-term babies ("term low birth weight"). Laurent et al. reported that a 5.82 $\mu g/m^3$ increase in PM2.5 exposures during pregnancy was linked to a 2.5% increased risk of term low birth weight (Laurent et al. 2014). The second study evaluated PM2.5 exposures by source, and found increased odds of term low birth weight with increased exposure to PM2.5 from diesel sources, gasoline, geological sources, as well as elemental carbon (Wilhelm et al. 2012).

Some newer research has also linked particulate matter exposures to risk of certain birth defects and stillbirth. A California-based study used monitoring station data and traffic density measures to evaluate potential associations with a variety of birth defects in the San Joaquin Valley (Padula et al. 2013a; Padula et al. 2013b; Padula et al. 2013c; Padula et al. 2015). One of these studies reported evidence suggesting that PM10 and PM2.5 may increase the risk of certain congenital heart defects (Padula et al. 2013b). For neural tube defects, increased risks were linked to higher exposures to carbon monoxide and nitrogen oxide (Padula et al. 2013a), but higher risks for spina bifida with PM10 exposures were found only among mothers living in lower socioeconomic status neighborhoods (Padula et al. 2015). An earlier study conducted in Los Angeles County used ambient monitoring data to estimate exposures, and reported increased

risk of certain congenital heart defects with higher exposures to carbon monoxide, but not for PM10; PM2.5 was not evaluated in this study (Ritz et al. 2002). A couple recent studies evaluated PM2.5 exposures during gestation and risk of stillbirth. A recent study conducted in Ohio used monitoring station data to evaluate stillbirth risk, and found that higher levels of PM2.5 exposure in the third trimester was linked to a 42% increased risk of stillbirth (DeFranco et al. 2015). A California-based study similarly found an increased risk of stillbirth with higher PM2.5 exposures averaged over the entire pregnancy, but the association may have been confounded by co-occurring nitrogen dioxide exposures (Green et al. 2015). A third study, conducted in Taiwan, found that higher PM10 and sulfur dioxide exposures in the first trimester were associated with increased risk of stillbirth among babies who were born preterm; PM2.5 was not assessed in this study (Hwang et al. 2011).

In the U.S. EPA review, it was noted that stronger associations with birth weight reductions are observed with PM2.5 compared to PM10, and animal toxicological studies provide supportive evidence, although a specific mechanism is not known (U.S. EPA 2009). These results and many other studies provide evidence that fetuses and infants are subgroups affected by particulate matter exposures.

Long-Term Particulate Matter Exposures and Newer Health Endpoints

Metabolic syndromes are relatively new health outcomes to be studied in relation to air pollution exposure. The U.S. EPA 2009 ISA reviewed only one epidemiological study and one toxicological study. These studies provided some evidence that particulate matter exposures may be linked to metabolic syndromes, such as insulin resistance, hypertension, high cholesterol, or obesity, or that having a metabolic syndrome may increase susceptibility to the effects of PM10 exposures on cardiovascular outcomes (U.S. EPA 2009).

Some recent studies have evaluated neurological impacts of PM2.5, including cognitive function in adults and autism spectrum disorder in children. A study conducted in the Los Angeles Basin used monitoring data to evaluate long-term exposures in a middle-aged and older adult population, and reported PM2.5 exposure was associated with decreased verbal learning (Gatto et al. 2014). Three recent studies reported that PM2.5 exposures during the prenatal period were associated with autism in childhood. One study was conducted in Los Angeles County, and reported that 7% increased odds of autism with a 4.68 $\mu g/m^3$ increase in PM2.5; the effect estimate increased to 15% when accounting for ozone in the statistical models (Becerra et al. 2013). A California-based study found that an 8.7 $\mu g/m^3$ increase in PM2.5 during the

prenatal period or in the first year of life doubled the odds of autism (Volk et al. 2013). The third study was based on the Nurses' Health Study II cohort, and reported an increased risk of autism with prenatal PM2.5 exposures, but not with exposures before pregnancy or after delivery (Raz et al. 2015). These studies provide emerging evidence of health effects of air pollution on neurological health outcomes.

Sensitive Populations for PM-Related Health Effects

Certain populations may be more sensitive to the health effects of particulate air pollution, and evidence to assess susceptibility comes from epidemiological, controlled human exposure, and toxicological studies of PM2.5 and PM10 exposures. The U.S. EPA 2009 ISA for PM concluded that there is evidence supporting increased susceptibility to the effects of PM among children and older adults, individuals with pre-existing cardiovascular or respiratory conditions, individuals with lower socioeconomic status (sometimes assessed using proxy measures such as educational attainment or residential location), and individuals with certain genetic polymorphisms that control antioxidant response, regulate enzyme activity, or regulate procoagulants (U.S. EPA 2009). In addition, there is some limited evidence that additional factors may increase a person's susceptibility to PM health effects, including chronic inflammatory conditions (e.g. diabetes, obesity) and life stage, with pregnant women and fetuses *in utero* being potentially more susceptible.

Summary - Particulate Matter Health Effects

Despite data gaps, the extensive body of epidemiological studies has both qualitative and quantitative consistency suggestive of causality. A considerable body of scientific evidence from these studies suggests that ambient particulate matter, alone or in combination with other coexisting pollutants, is associated with increases in mortality and morbidity in a community. The evidence for particulate matter effects is mostly derived from population studies with supportive evidence from clinical and animal studies. Although most of the effects are attributable to particulate matter, co-pollutant effects cannot be ruled out on the basis of existing studies. The difficulty of separating the effects may be due to the fact that particulate levels co-vary with other combustion source pollutants. That is, the particle measurements serve as an index of overall exposure to combustion-related pollution, and some component(s) of combustion pollution other than particles might be at least partly responsible for the observed health effects. Many research studies, including some recent studies, have evaluated the health effects of exposures to air pollutants from traffic emissions using a variety of exposure modeling techniques (Hart et al. 2014; Harris et al. 2015; Kingsley et al.

2015; Rice et al. 2015; Danysh et al. 2016). In general, these articles are not discussed in detail here, because of the difficulty in attributing the observed effects to a specific pollutant or combination of pollutants. However, these studies do provide supporting evidence that air pollutants from traffic exhaust are linked to health effects in humans.

With measures adopted to control emissions of air pollutants, ambient levels of PM2.5 have been decreasing. These reductions in particulate matter have been associated with reductions in mortality. For example, studies have found that increases in life expectancy are associated with reductions in air pollution levels, and that a portion of this increase can be attributed to reductions in PM2.5 exposures (Correia et al. 2013; Pope et al. 2013).

In terms of estimating health burdens of air pollution exposure, CARB has conducted analyses in the past estimating exposures and quantitative health effects from exposures to particulate matter as well as other pollutants. A recent assessment focused on premature mortality and PM2.5 (California Air Resources Board 2010). The analysis used the U.S. EPA's risk assessment methodology for calculating premature mortality and used ambient air quality measurements averaged over a three-year period of 2006-2008. An update to this analysis using ambient air quality data from 2009-2011 indicated that PM2.5-related premature deaths in California due to cardiopulmonary causes as 7,200 deaths per year with an uncertainty range of 5,600 – 8,700. Estimates were also made for the California Air Basins. For the South Coast Air Basin, the estimate was 4,000 cardiopulmonary deaths per year with an uncertainty range of 3,200–4,900. These estimates were calculated using the associations of cardiopulmonary mortality and PM2.5 from the second exposure period from Krewski (Krewski et al. 2009).

Another analysis of health impacts in the South Coast was conducted as part of the Socioeconomic Report for the 2012 AQMP. The analysis estimated the anticipated costs and benefits of adopting the measures in the Final 2012 AQMP, which included the projected public health benefits associated with lower PM2.5 concentrations as a result of the 2012 plan. Based on that analysis, the annual health benefit of the 2012 AQMP was projected to reach $1.7 billion in 2023, with the majority of the health benefits attributed to averted deaths due to PM2.5 reductions (South Coast Air Quality Management District 2012).

ULTRAFINE PARTICLES

As noted above, numerous studies have found associations between particulate matter levels and adverse health effects, including mortality, hospital admissions, and respiratory disease symptoms. The vast majority of these studies used particle mass of PM10 or PM2.5 as the measure of exposure. Some researchers have postulated, however, that ultrafine particles may be responsible for some of the observed associations of particulate matter and health outcomes (Oberdorster et al. 1995; Seaton et al. 1995). Ultrafine particles are typically defined as particles with aerodynamic diameters of less than 0.1 µm or 100 nm. Ultrafine particles are formed as a result of combustion processes as well as secondary atmospheric transformations. Vehicle emissions, especially diesel exhaust, are major sources of ultrafine particles; therefore, proximity to a major roadway is an important factor that affects an individual's exposure to ultrafine particles (Zhu et al. 2002; HEI Review Panel on Ultrafine Particles 2013). There is currently no federal or California standard for ultrafine particles.

U.S. EPA staff has presented conclusions on causal determination of several health effects of ultrafine PM based on a recent review of the available scientific studies (U.S. EPA 2009). These are depicted in Table I-9.

TABLE I-9

Summary of Causal Determination of Ultrafine PM by Exposure Duration and Health Outcome

SHORT-TERM EXPOSURES	
Health Outcome	**Causality Determination**
Cardiovascular effects	Suggestive of a causal relationship
Respiratory effects	Suggestive of a causal relationship
Central nervous system	Inadequate to infer a causal relationship
Mortality	Inadequate to infer a causal relationship
LONG-TERM EXPOSURES	
Health Outcome	**Causality Determination**
Cardiovascular effects	Inadequate to infer a causal relationship
Respiratory effects	Inadequate to infer a causal relationship
Mortality	Inadequate to infer a causal relationship

Reproductive and developmental	Inadequate to infer a causal relationship
Cancer, Mutagenicity, Genotoxicity	Inadequate to infer a causal relationship

(From (U.S. EPA 2009) Table 2-4 and Chapters 6 and 7)

Several potential mechanisms have been brought forward to suggest that the ultrafine portion may be important in determining the toxicity of ambient particulates, some of which are discussed below.

For a given mass concentration, ultrafine particles have much higher numbers of particles and surface area compared to larger particles. Particles can act as carriers for other adsorbed agents, such as trace metals and organic compounds; and the larger surface area may transport more of such toxic agents than larger particles.

Smaller particles can also be inhaled deeper into the lungs, although the relationship between deposition fraction and particle size is complex. The ultrafine particles between 20-30 nm generally have higher fractional deposition in the alveolar region of the lung, where air exchange takes place. Because ultrafine particles are cleared from the lung more slowly compared to larger particles, the ultrafine particles can accumulate in the lung tissue where they can also translocate into the blood and to other organs (HEI Review Panel on Ultrafine Particles 2013).

Exposures of laboratory animals to ultrafine particles have found cardiovascular and respiratory effects. Using an animal model of atherosclerotic disease, mice exposed to concentrated ultrafine particles (defined as less than 0.18 µm) near a roadway in Southern California showed larger early atherosclerotic lesions than mice exposed to concentrated PM2.5 or to filtered air (Araujo et al. 2008). In a mouse allergy model, exposures to concentrated ultrafine particles (less than 0.18 µm) resulted in a greater response to antigen challenge to ovalbumin (Li et al. 2010), indicating that vehicular traffic exposure could exacerbate allergic inflammation in already-sensitized animals.

Controlled exposures of human volunteers to very high levels of ultrafine particles either laboratory generated or as products of combustion, such as diesel exhaust containing particles, have found physiological changes related to vascular effects. Mills et al., for example found exposure to diesel exhaust particulate attenuated both acetylcholine and sodium-nitroprusside-induced vasorelaxation (Mills et al. 2011), although these exposures were at levels much higher than ambient concentrations. This study showed that diesel exhaust particulates had impacts on vascular function while carbon nanoparticles did not change vascular function, providing evidence that is complementary to the epidemiological studies linking particulate matter exposure to cardiovascular outcomes.

A recent review of the health effects of ultrafine particles concluded that current available evidence does not support that exposures to ultrafine particles alone account for the adverse health effects that have been associated with other ambient pollutants such as PM2.5, although the report noted several limitations in the exposure data relating to ultrafine particles (HEI Review Panel on Ultrafine Particles 2013).

There is a lack of long-term studies of human population exposure to ultrafine particles, as there is currently no ultrafine monitoring network in the U.S. As noted above, however, a recent study from California estimated exposures to PM2.5 and ultrafine particles among members of the California Teachers Study cohort. Positive, statistically significant associations of ischemic heart disease mortality were observed with modeled PM2.5 and with ultrafine particle mass concentrations derived from chemical transport models using California emissions inventories (Ostro et al. 2015).

There have been several cross-sectional epidemiological studies of ultrafine particles, mainly from Europe. Some of these studies found effects on hospital admissions and emergency department visits for respiratory and cardiovascular effects, whereas other studies did not find such effects (U.S. EPA 2009). Concentrations of ultrafine particles can vary geographically, and it is not clear how well the central-site monitors used in these studies reflect actual exposures.

Additional discussion on the sources and health effects of ultrafine particles can be found in Chapter 9 of the 2012 AQMP.

CARBON MONOXIDE

Carbon monoxide (CO) is a gaseous air pollutant that has a high affinity to bond with oxygen-carrying proteins (hemoglobin and myoglobin). The resulting reduction in oxygen supply in the bloodstream is responsible for the toxic effects of CO, which are typically manifested in the oxygen-sensitive organ systems. The effects have been studied in controlled laboratory environments involving exposure of humans and animals to CO, as well as in population-based studies of ambient CO exposure effects. People with deficient blood supply to the heart (ischemic heart disease) are known to be susceptible to the effects of CO. Protection of this group is the basis of the existing National Ambient Air Quality Standards for CO at 35 ppm for one hour and 9 ppm averaged over eight hours. The health effects of ambient CO have been recently reviewed by U.S. EPA, with the strongest evidence supporting a likely causal link between short-term CO exposures and cardiovascular outcomes, although studies have

linked both short-term and long-term CO exposures to several other health outcomes (Table I-10) (U.S. EPA 2010).

TABLE I-10

Causal Determination for Health Effects of Carbon Monoxide

SHORT-TERM EXPOSURES	
Health Outcome	**Causality Determination**
Cardiovascular morbidity	Likely to be a causal relationship
Central nervous system	Suggestive of a causal relationship
Respiratory morbidity	Suggestive of a causal relationship
Mortality	Suggestive of a causal relationship
LONG-TERM EXPOSURES	
Health Outcome	**Causality Determination**
Cardiovascular morbidity	Inadequate to infer a causal relationship
Central nervous system	Suggestive of a causal relationship
Birth outcomes and developmental effects	Suggestive of a causal relationship
Respiratory morbidity	Inadequate to infer a causal relationship
Mortality	Not likely to be a causal relationship

(From (U.S. EPA 2010) Table 2-1)

Inhaled CO has no known direct toxic effect on lungs but rather exerts its effects by interfering with oxygen transport—through the formation of carboxyhemoglobin (COHb, a chemical complex of CO and hemoglobin)), which reduces the amount of oxygen the blood can carry to the tissues. Exposure to CO is often evaluated in terms of COHb levels in blood, measured as percentage of total hemoglobin bound to CO. Endogenous COHb is estimated to be <1% in healthy individuals, but COHb levels are sensitive to health status and metabolic state, with higher levels among smokers and persons with inflammatory diseases. Estimates based on a large prospective study of adults conducted in the 1970s showed a dose-response relationship between the average number of cigarettes smoked per day and the COHb concentrations (never smokers: 1.59±1.72%, former smokers: 1.96±1.87%, 1-5 cigarettes/day: 2.31±1.94%, 6-14 cigarettes/day: 4.39±2.48%, 15-24 cigarettes/day: 5.68±2.64%, >=25 cigarettes/day: 6.02±2.86%) (Hart et al. 2006).

Under controlled laboratory conditions, healthy subjects exposed to CO sufficient to result in 5% COHb levels exhibited reduced duration of maximal exercise performance due to the inability to deliver sufficient oxygen to the heart and other muscles. Studies involving subjects with coronary artery disease who engaged in exercise during CO exposures have shown that COHb levels as low as 2.4% can lead to earlier onset of electrocardiograph changes indicative of deficiency of oxygen supply to the heart. Other effects of inadequate oxygen delivery to the body tissues include earlier onset of chest pain, increase in the duration of chest pain, headache, confusion and drowsiness (U.S. EPA 2000).

A number of epidemiological studies have found associations between short-term ambient CO levels and increased hospital admissions and emergency department visits for ischemic heart disease, including myocardial infarction (U.S. EPA 2010). In studies reporting results stratified by age and sex, larger effects were generally observed among older adults and among males. Examples of such studies, including information on number of days of lag time between exposure and hospital admissions for key cardiovascular outcomes, are shown in the figure below.

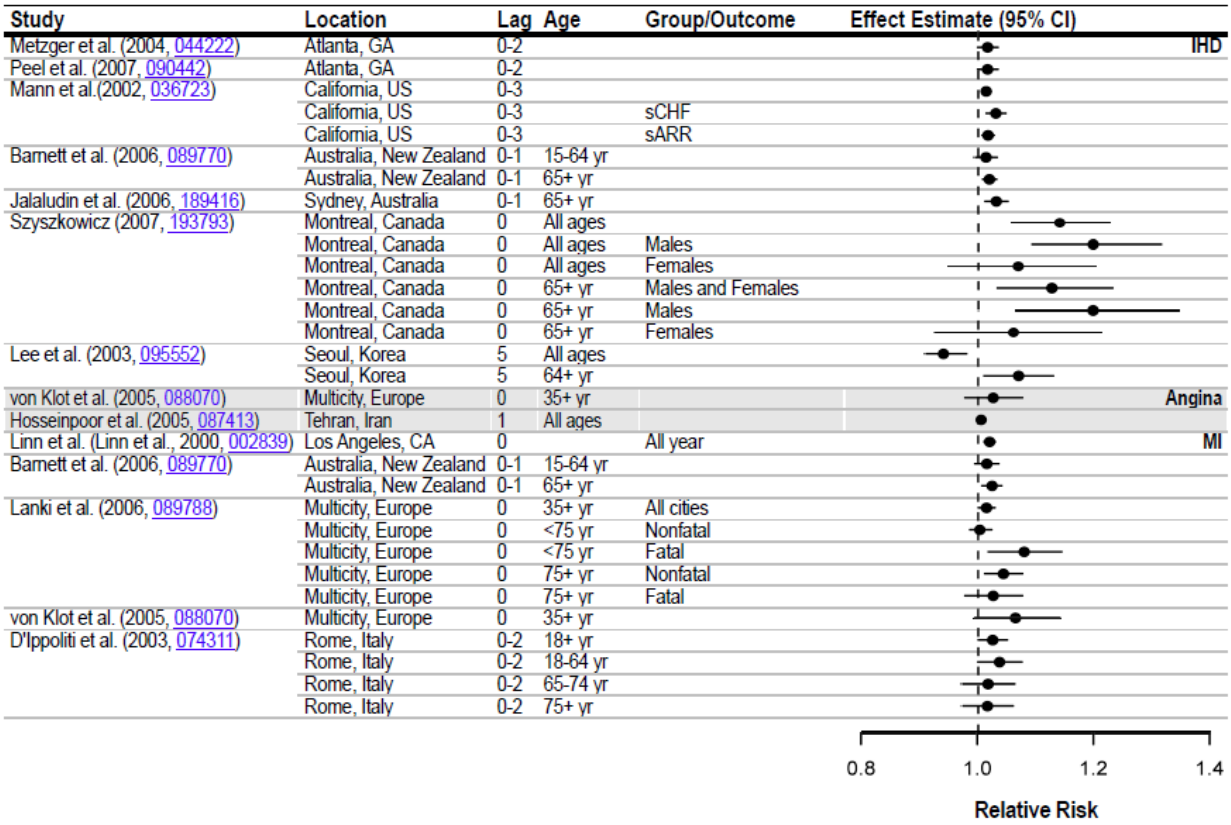


FIGURE I-8

Effect estimates (95% confidence intervals) associated with hospital admissions for various forms of heart disease. Effect estimates have been standardized to a 1 ppm increase in ambient CO for 1-h max CO concentrations, 0.75 ppm for 8-h max CO concentrations, and 0.5 ppm for 24-h avg CO concentrations (From (U.S. EPA 2010), Figure 5-2). Lag time is the time between the exposure and the outcome measured. The closed circle on the diagram indicates the effect estimate, while the bar indicates the 95% confidence interval.

Research studies have also evaluated ambient CO exposures in relation to reproductive health outcomes. Epidemiological studies conducted in Southern California have reported an association between with CO exposure during pregnancy and increases in pre-term births (Ritz et al. 2000; Wilhelm et al. 2005; Ritz et al. 2007). The increases in the pre-term births were also associated with PM10 or PM2.5 levels. There are very few studies examining CO exposure and birth defects, but one Southern California study found increased risks for cardiac-related birth defects with carbon monoxide exposure in the second month of pregnancy (Ritz et al. 2002). Toxicological studies in laboratory animals with higher than ambient levels of CO have also reported decrements in birth weight and prenatal growth, as well as impaired neurobehavior in the offspring of exposed animals (U.S. EPA 2010). The U.S. EPA concluded in their most recent review that the evidence linking long-term CO exposures with reproductive health outcomes was suggestive of a causal relationship.

NITROGEN DIOXIDE

Nitrogen dioxide (NO_2) is a gaseous air pollutant that serves as an indicator of gaseous oxides of nitrogen, such as nitric oxide (NO) and other related compounds (NO_x). Evidence of the health effects of NO_2 is derived from human and animal studies, which link NO_2 with respiratory effects such as decreased lung function and increases in airway responsiveness and pulmonary inflammation (U.S. EPA 2016). The U.S. EPA in 2010 retained the existing standards of 53 ppb for NO_2 averaged over one year, and adopted a new short-term standard of 100 ppb (0.1 ppm) averaged over one hour. The standard was designed to protect against increases in airway reactivity in individuals with asthma based on controlled exposure studies, as well as respiratory symptoms observed in epidemiological studies. The revised standard also requires additional monitoring for NO_2 near roadways.

In the current U.S. EPA Integrated Science Assessment for Nitrogen Oxides (U.S. EPA 2016), the staff conclusion for causal relationships between exposures and health effects are shown in the following table.

TABLE I-11

Causal Determination for Health Effects of Nitrogen Dioxide

SHORT-TERM EXPOSURES	
Health Outcome	**Causality Determination**
Respiratory effects	Causal relationship
Cardiovascular and related metabolic effects	Suggestive of a causal relationship
Total mortality	Suggestive of a causal relationship
LONG-TERM EXPOSURES	
Health Outcome	**Causality Determination**
Respiratory effects	Likely to be a causal relationship
Cardiovascular and related metabolic effects	Suggestive of a causal relationship
Reproductive and developmental effects	Fertility, Reproduction, and Pregnancy: Inadequate to infer a causal relationship Birth Outcomes: Suggestive of a causal relationship Postnatal Development: Inadequate to infer a causal relationship
Total Mortality	Suggestive of a causal relationship
Cancer	Suggestive of a causal relationship

(From (U.S. EPA 2016), Table ES-1)

Since the previous U.S. EPA Integrated Science Assessment (ISA) for Nitrogen Oxides from 2008, the causal determination for short-term and long-term respiratory effects have been updated in the 2016 ISA to reflect the stronger evidence now available pointing to a causal or likely causal relationship. For non-respiratory outcomes, the U.S. EPA also updated their assessment of the weight of evidence to show that the evidence for several short- and long-term outcomes is suggestive, but not sufficient to infer a causal relationship. Evidence for low-level nitrogen dioxide (NO_2) exposure effects is derived from laboratory studies of asthmatics and from epidemiological studies. Additional evidence is derived from animal studies. In the 2016 ISA, the U.S. EPA cited the coherence of the results from a variety of studies, and a plausible biological mechanism (whereby NO2 reacts with the respiratory lining and forms secondary oxidation products that increase airway responsiveness and allergic inflammation) to support the determination of a causal relationship between short-term

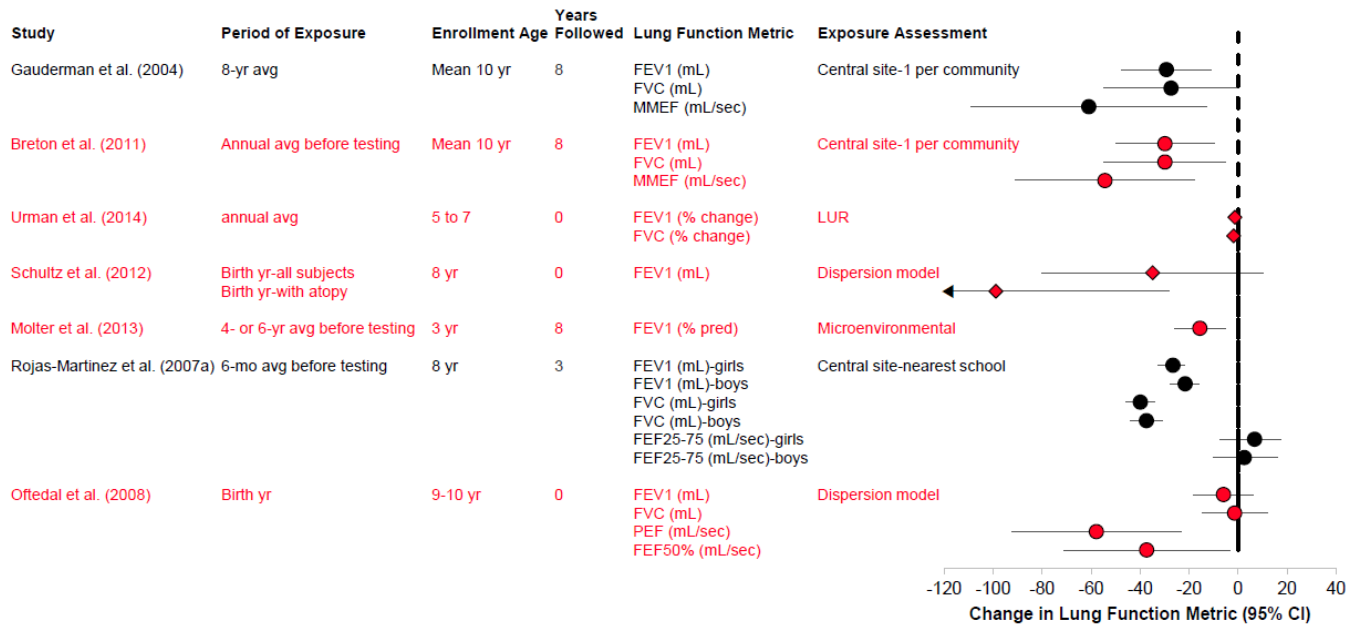
NO_2 exposures and asthma exacerbations ("asthma attacks"). The long-term link with respiratory outcomes was strengthened by recent experimental and epidemiological studies, and the strongest evidence available is from studies of asthma development.

Several studies related to outdoor exposure have found health effects associated with ambient NO_2 levels, including respiratory symptoms, respiratory illness, decreased lung function, pulmonary inflammation, increased emergency room visits for asthma, and cardiopulmonary mortality. However, since traffic exhaust is an important source of NO_2 and several other pollutants, such as particulate matter, exposure generally occurs in the presence of other pollutants, making it more difficult for these studies to distinguish the specific role of NO_2 in causing effects independent of other pollutants. However, studies linking NO_2 to asthma exacerbations and human experimental studies provided support for the U.S. EPA determination that this causal relationship exists for short-term NO_2 exposures independent of other traffic-related pollutants (U.S. EPA 2016). The report also concludes that epidemiological studies do not rule out the possible influence of other traffic-related pollutants on the observed health effects.

The Children's Health Study in Southern California has evaluated a variety of health endpoints in relation to air pollution exposures, including lung function, lung development, school absences, and asthma. The study found associations between long-term exposure to air pollution, including NO_2, PM10, and PM2.5, and respiratory symptoms in asthmatic children (McConnell et al. 1999). Particles and NO_2 levels were correlated, and independent effects of individual pollutants could not be discerned. A subsequent analysis using more refined exposure estimation methods indicated consistent associations between long-term NO_2 exposures and respiratory symptoms in children with asthma (McConnell et al. 2003).

Ambient levels of NO_2 were also associated with a decrease in lung function growth in a group of children followed for eight years, including children with no history of asthma. In addition to NO_2, the decreased growth was also associated with particulate matter and airborne acids. The study authors postulated this may be a result of a package of pollutants from traffic sources (Gauderman et al. 2004).

A number of studies have since reported deficits in lung function associated with nitrogen oxides exposures. Examples are shown in Figure I-9.



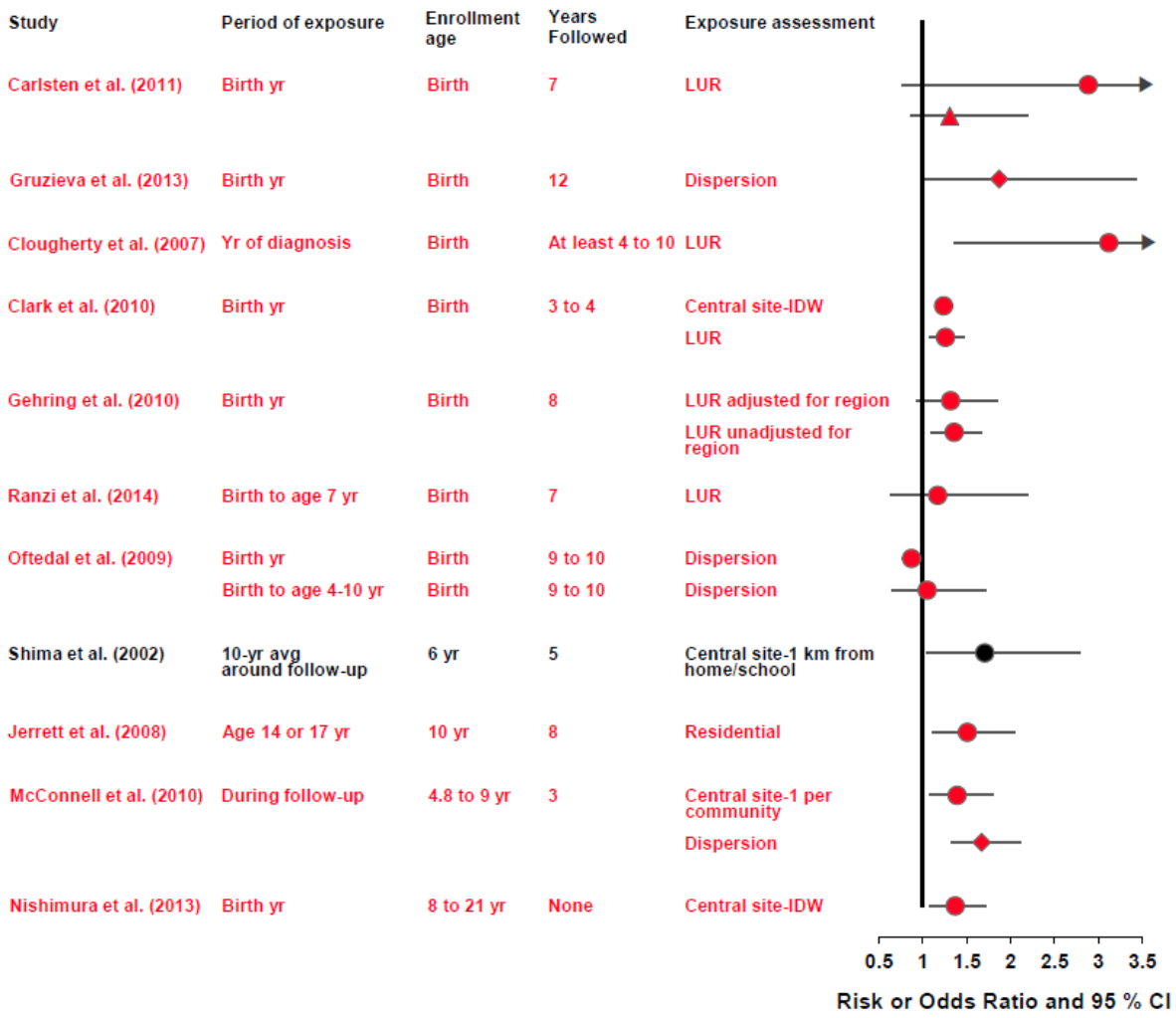
Note: Studies in red are recent studies. Studies in black were included in the 2008 ISA for Oxides of Nitrogen. Circles = NO_2; Diamonds = NO_x. All mean changes in this plot are standardized to a 10-ppb increase in NO_2 and a 20-ppb increase in NO_x concentration. Effect estimates from studies measuring NO_x in $\mu g/m^3$ (Schultz et al., 2012) have not been standardized.

FIGURE I-9

Associations of nitrogen dioxide (NO_2) or the sum of nitric oxide and NO_2 (NOx) with lung function indices from prospective studies of children (From (U.S. EPA 2016), Figure 6-5).

A follow-up report from the Children's Health Study has assessed whether improving air quality in Southern California over the past several decades has led to beneficial changes in health among children (Gauderman et al. 2015). It was reported that as the levels of nitrogen oxide and fine particulates came down as the result of air pollution emissions reductions, the deficits in lung function growth were also of a smaller magnitude. Such improvements were observed in children with asthma as well as in those without asthma. These results indicate that improvements in air quality are associated with improvements in children's health.

In recent years, the most compelling evidence of long-term effects of NO_2 has been from prospective cohort studies that link NO_2 exposures to the development of asthma, primarily in children. The U.S. EPA included several recent studies in their review, as shown in the Figure I-10. The vast majority of these studies found that higher NO2 exposures were linked to an increased risk or odds of developing asthma among children.



Effect estimates are standardized to a 10-ppb increase in NO_2, with the exception of Gruzieva et al. (2013) who examined NOx in µg/m3 and Oftedal et al (2009) who did not report increments for the effect estimates for the birth to age 4 years or birth to age 10 years exposure periods. Note: Black symbols = studies evaluated in the 2008 Integrated Science Assessment for Oxides of Nitrogen; Red symbols = recent studies. Circles=NO_2; triangles=NO; diamonds=NOx.

FIGURE I-10

Associations of ambient nitrogen dioxide (NO_2) concentrations with asthma incidence in longitudinal cohort studies of children (From (U.S. EPA 2016), Figure 6-1).

Among the studies of childhood asthma incidence reviewed in the 2016 U.S. EPA ISA for Oxides of Nitrogen, two studies were conducted in Southern California. Both studies were based on the Children's Health Study cohort, but one study used a smaller subset of the cohort and estimated NO_2 exposures using monitors at the children's homes (Jerrett et al. 2008). The second study examined over 2000 children and used data from air monitoring stations as well as modeled NO_2 levels to estimate exposures

(McConnell et al. 2010). Both studies found a positive association between NO_2 exposures and the onset of asthma in these children, however, because NO_2 is often strongly correlated with PM2.5 and other components of traffic-related air pollution, it is possible that the effects observed are due to some other component of traffic exhaust for which NO_2 serves as a proxy measure. The consistency of the effects found linking NO_2 exposure and asthma development in children, the use of prospective longitudinal study designs following children for several years, and the use of several different methods to estimate exposures are noted strengths of such studies. Experimental studies have found that NO_2 exposures increase responsiveness of airways, pulmonary inflammation, and oxidative stress, and can lead to the development of allergic responses. These biological responses provide evidence of a plausible mechanism for NO_2 to cause asthma.

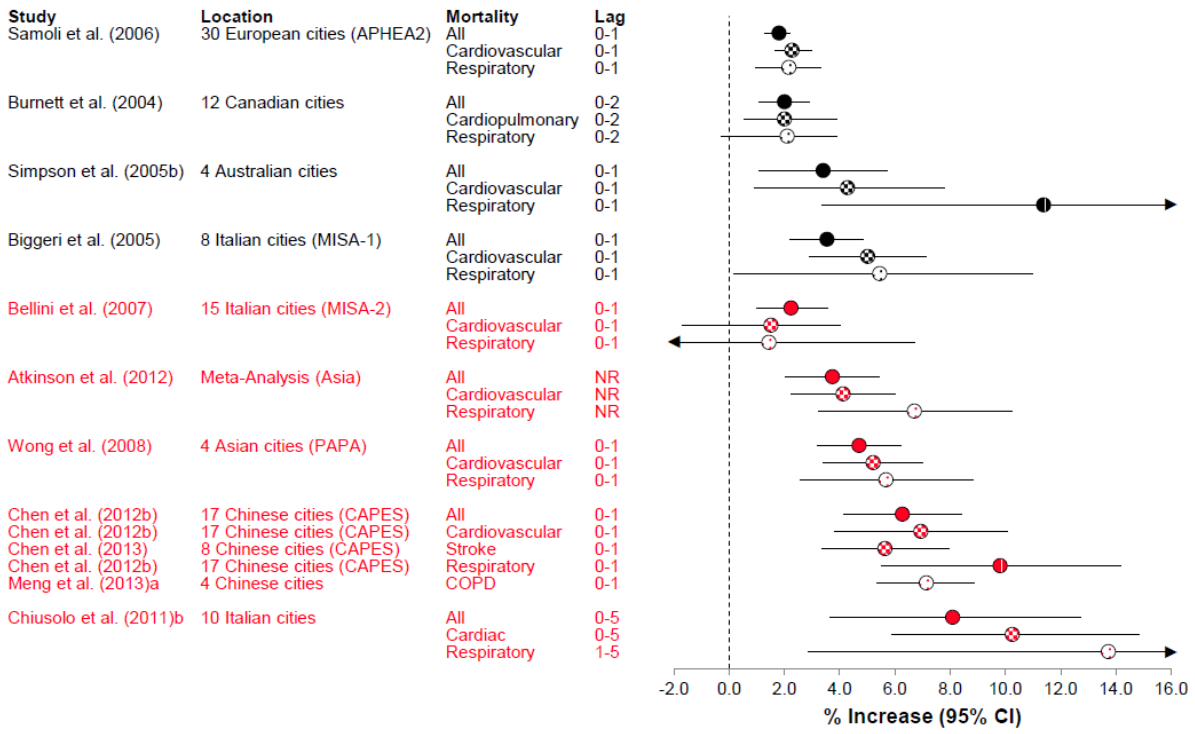
Results from controlled exposure studies of asthmatics demonstrate an increase in the tendency of airways to contract in response to a chemical stimulus (airway responsiveness) or after inhaled allergens (U.S. EPA 2016). Effects were observed among adult volunteers with asthma when exposed to 100 ppb NO_2 for 60 minutes and to 200-300 ppb for 30 minutes, with approximately 70% of study participants experiencing an increase in airway responsiveness. A similar response was reported in some studies with healthy subjects at higher levels of exposure (1.5 - 2.0 ppm), although these changes in healthy adults are likely of little or no clinical significance. Increased airway responsiveness among people with asthma can lead to worse symptoms and reduced lung function. Mixed results have been reported when people with chronic obstructive lung disease are exposed to low levels of NO_2.

Short-term controlled studies of rats exposed to NO_2 over a period of several hours indicate cellular changes associated with allergic and inflammatory responses that can lead to liver damage and reduced hepatic function. Rodent models exposed to NO_2 repeatedly for 4 to 14 days demonstrated increased airway responsiveness with high levels of exposure. Animal studies also provide evidence that NO_2 exposures have negative effects on the immune system, and therefore increase the host's susceptibility to respiratory infections. Epidemiological studies showing associations between NO_2 levels and hospital admissions for respiratory infections also support such a link (U.S. EPA 2016).

Several epidemiological studies conducted in California have examined associations between NO_2 exposures and other health effects, including some recent studies evaluating cardiovascular effects (Coogan et al. 2012; Bartell et al. 2013; Wittkopp et al. 2013), mortality (Lipsett et al. 2011; Bartell et al. 2013; Jerrett et al. 2013), birth

outcomes (Ghosh et al. 2012; Laurent et al. 2014; Padula et al. 2014; Ritz et al. 2014; Green et al. 2015), and cancer (Ghosh et al. 2013). Many other studies conducted in other geographic areas have found links with these health outcomes (U.S. EPA 2016). In addition, some of the newer outcomes evaluated in relation to NO_2 exposures include neurological outcomes such as Parkinson's disease (Ritz et al. 2016), Alzheimer's disease (Oudin et al. 2016), and autism (Becerra et al. 2013; Volk et al. 2013), as well as metabolic diseases such as diabetes and obesity (Coogan et al. 2012; Robledo et al. 2015; White et al. 2016). However, many of these studies use NO_2 exposures as a proxy measure for traffic-related air pollutants, and do not aim to identify a specific pollutant within the mix of pollutants from this source. Thus, there is uncertainty on whether NO_2 exposure has independent relationships with non-respiratory related health effects.

Examples of studies reporting an association of mortality with short-term NO_2 exposures are shown in the figure below.



Note: Black symbols = multicity studies evaluated in the 2008 Integrated Science Assessment for Oxides of Nitrogen; Red symbols = recent studies. Filled circle = total mortality; Crosshatch = cardiovascular mortality; Vertical lines = respiratory mortality.

FIGURE I-11

Percentage increase in total, cardiovascular, and respiratory mortality from multi-city studies for a 20-ppb increase in 24-hour average or 30-ppb increase in one-hour maximum nitrogen dioxide concentrations (From (U.S. EPA 2016), Figure 5-23).

SULFUR DIOXIDE

Sulfur dioxide (SO2) is a gaseous air pollutant that has been linked to a variety of respiratory effects, such as decreased lung function and increased airway resistance. Controlled laboratory studies involving human volunteers have clearly identified asthmatics as a very sensitive group to the effects of ambient sulfur dioxide (SO_2) exposures. Healthy subjects have failed to demonstrate any short-term respiratory functional changes at exposure levels up to 1.0 ppm over 1-3 hours. In exercising asthmatics, brief exposure (5-10 minutes) to SO_2 at levels between 0.2-0.6 ppm can result in increases in airway resistance and decreases in breathing capacity. The response to SO_2 inhalation is observable within two minutes of exposure, increases further with continuing exposure up to five minutes, then remains relatively steady as exposure continues. SO_2 exposure is generally not associated with any delayed reactions or repetitive asthmatic attacks (U.S. EPA 2008). In 2010, the U.S. EPA SO_2 air quality standard was set at 75 ppb (0.075 ppm) averaged over one hour to protect against acute asthma attacks in sensitive individuals.

The EPA assessment based on the 2008 Integrated Science Assessment for Sulfur Oxides is shown in the table below (U.S. EPA 2008). The U.S. EPA recently released a draft of the revised ISA for SO2 (U.S. EPA 2015a) which evaluates recent evidence assessing links to mortality and cardiovascular, respiratory, carcinogenic, and reproductive effects (Brunekreef et al. 2009; Hart et al. 2011; Pascal et al. 2013; Chen et al. 2014; Gianicolo et al. 2014; Milojevic et al. 2014; Moridi et al. 2014; Stingone et al. 2014; Straney et al. 2014; Wang et al. 2014; Winquist et al. 2014; Yang et al. 2014; Ancona et al. 2015; Green et al. 2015; Rich et al. 2015; Shah et al. 2015; Yorifuji et al. 2015).

TABLE I-12

Causal Determinations for Health Effects of Sulfur Oxides

SHORT-TERM EXPOSURES	
Health Outcome	**Causality Determination**
Respiratory morbidity	Causal relationship
Cardiovascular morbidity	Inadequate to infer a causal relationship
Mortality	Suggestive of a causal relationship
LONG-TERM EXPOSURES	

Health Outcome	Causality Determination
Respiratory morbidity	Inadequate to infer a causal relationship
Carcinogenic effects	Inadequate to infer a causal relationship
Prenatal and neonatal outcomes	Inadequate to infer a causal relationship
Mortality	Inadequate to infer a causal relationship

(From (U.S. EPA 2008) Chapter 3)

In epidemiologic studies of children and adults, associations of short-term variations in SO_2 levels with increases in respiratory symptoms, emergency department visits, and hospital admissions for respiratory-related causes have been reported. There is uncertainty as to whether SO_2 is associated with the effects or whether other co-occurring pollutants may explain the observed effects, although some studies indicated that the SO_2 effects remained even after accounting for the effects of other pollutants, including PM2.5. Coupled with the human clinical studies, these data suggest that SO_2 can trigger asthmatic episodes in individuals with pre-existing asthma (U.S. EPA 2008).

Animal studies have shown SO_2 effects on pulmonary inflammation with acute exposure at concentrations consistent with ambient SO_2 levels. Toxicological studies using animals found that repeated exposures to concentrations of SO_2 as low as 0.1 ppm promoted allergic sensitization and airway inflammation. Such evidence, combined with human clinical studies and epidemiological studies in people with asthma support the U.S. EPA determination of a causal relationship between short-term SO_2 exposure and respiratory morbidity. One of these studies was conducted in the Los Angeles area, and found that higher ambient SO_2 levels were associated with increased odds of asthma symptoms among Hispanic children with asthma (Delfino et al. 2003).

Some epidemiological studies indicate that the cardiovascular mortality effects associated with short-term exposures to ambient SO_2 were generally reduced when accounting for other pollutants, although the evidence is still suggestive of a causal relationship. Few epidemiological studies are available to assess the potential confounding effects of other co-occurring pollutants in studies of long-term effects. For example, there is some evidence that sulfates, which are formed when SO_2 oxidizes rapidly in the atmosphere, may be associated with lung function changes, although the evidence is not consistent (Reiss et al. 2007). Sulfates are positively correlated with SO_2 levels, so it is difficult to distinguish the effect of one individual pollutant. Based on a level determined necessary to protect the most sensitive

individuals, the California Air Resources Board (CARB) in 1976 adopted a standard of 25 µg/m^3 (24-hour average) for sulfates. There is no federal air quality standard for sulfates.

LEAD

Lead (Pb) is a toxic air contaminant that is recognized to exert an array of deleterious effects on multiple organ systems. There are a number of potential public health effects at low level exposures. The health implications are generally indexed by blood lead levels which are related to lead exposures both from inhalation as well as from ingestion. Effects include impacts on population IQ as well as heart disease and kidney disease. The initial air quality standard for lead was established by U.S. EPA in 1978 at a level of 1.5 µg /m^3 averaged over a calendar quarter. U.S. EPA revised the NAAQS for lead in 2008 to a level of 0.15 µg/m^3 averaged over a rolling three-month period to protect against lead toxicity.

The U.S. EPA has recently reviewed the health effects of ambient lead exposures in conjunction with an Integrated Science Assessment and a review of the NAAQS for lead (U.S. EPA 2013a; U.S. EPA 2015c). The following table gives the summary of causality conclusions from the U.S. EPA review.

TABLE I-13

Summary of Causal Determinations for the Relationship Between Exposure to Pb and Health Effects

HEALTH OUTCOME	CAUSALITY DETERMINATION
Children - Nervous System Effects	
Cognitive Function Decrements	Causal relationship
Externalizing Behaviors: Attention, Impulsivity and Hyperactivity	Causal relationship
Externalizing Behaviors: Conduct Disorders in Children and Young Adults	Likely to be a causal relationship
Internalizing Behaviors	Likely to be a causal relationship
Auditory Function Decrements	Likely to be a causal relationship
Visual Function Decrements	Inadequate to infer a causal relationship
Motor Function Deficits	Likely to be a causal relationship

Adults – Nervous System Effects	
Cognitive Function Decrements	Likely to be a causal relationship
Psychopathological Effects	Likely to be a causal relationship
Cardiovascular effects	
Hypertension	Causal relationship
Subclinical Atherosclerosis	Suggestive of a causal relationship
Coronary Heart Disease	Causal relationship
Cerebrovascular Disease	Inadequate to infer a causal relationship
Renal Effects	
Reduced Kidney Function	Suggestive of a causal relationship
Immune System Effects	
Atopic and Inflammatory Response	Likely to be a causal relationship
Decreased Host Resistance	Likely to be a causal relationship
Autoimmunity	Inadequate to infer a causal relationship
Hemotologic Effects	
Decreased Red Blood Cell Survival and Function	Causal relationship
Altered Heme Synthesis	Causal relationship
Reproductive and Developmental Effects	
Development	Causal relationship
Birth Outcomes (low birth weight, spontaneous abortion)	Suggestive of a causal relationship
Male Reproductive Function	Causal relationship
Female Reproductive Function	Suggestive of a causal relationship
Cancer	
Cancer	Likely to be a causal relationship

(From (U.S. EPA 2013a) Table ES-1)

Children appear to be sensitive to the neurological toxicity of lead, with effects observed at blood lead concentration ranges of 2 – 8 µg/dL. No clear threshold has been established for such effects. According to the U.S. EPA review, the most important effects observed are neurotoxic effects in children and cardiovascular effects in adults. The effects in children include impacts on intellectual attainment and school performance. Figure I-12 provides a summary of the lowest levels of blood lead that

have been associated with certain neurological, hematological and immune effects in children.

Lowest Observed Effect Blood Lead Level	Neurological Effects	Hematological Effects	Immune Effects
30 µg/dL		Increased urinary δ-aminolevulinic acid	
15 µg/dL	Behavioral disturbances (e.g., inattention, delinquency) Altered electrophysiological responses	Erythrocyte protoporphyrin (EP) elevation	
10 µg/dL	Effects on neuromotor function CNS cognitive effects (e.g., IQ deficits)	Inhibition of δ-aminolevulinic acid dehydratase (ALAD) | Pyrimidine-5′-nuclotidase (Py5N) activity inhibition	Effects on humoral (↑ serum IgE) and cell-mediated (↓ T-cell abundance) immunity
5 µg/dL	↓	↓	
	(???)	(???)	
0 µg/dL			

Note: Arrows depict cases where weight of overall evidence strongly substantiates likely occurrence of type of effect in association with blood-Pb concentrations in range of 5-10 µg/dL, or possibly lower, as implied by (???). Although no evident threshold has yet been clearly established for those effects, the existence of such effects at still lower blood-Pb levels cannot be ruled out based on available data.

Source: Adapted/updated from Table 1-17 of U.S. Environmental Protection Agency (1986a).

FIGURE I-12

Summary of Lowest Observed Effect Levels for Key Lead-Induced Health Effects in Children (From (U.S. EPA 2007), Table 3-1)

Figures I-12 and I-13, taken from the U.S. EPA review (U.S. EPA 2007), depict the health effects of lead in relation to blood levels. In the figure, the question marks indicate that there are no demonstrated threshold blood lead levels for health effects. The Centers for Disease Control (CDC) has recently revised their lead hazard information and replaced their level of concern for adverse effects of 10 µg/dL blood lead level with a childhood blood lead level reference value of 5 µg/dL to identify children and environments associated with lead-exposure hazards (Centers for Disease Control and Prevention 2016).

Figure I-13 provides a summary of the lowest levels of blood lead that have been associated with key health effects in adults. For adults, evidence supports a causal relationship between lead and increased blood pressure and hypertension, as well as coronary heart disease (myocardial infarction, ischemic heart disease, and heart rate

variability). Other health effects among adults are also relatively high on the causal scale, including neurological, hematological, and renal effects.

Lowest Observed Effect Blood Lead Level	Neurological Effects	Hematological Effects	Cardiovascular Effects	Renal Effects
30 µg/dL	Peripheral sensory nerve impairment	Erythrocyte protoporphyrin (EP) elevation in males		Impaired Renal Tubular Function
20 µg/dL	Cognitive impairment			
15 µg/dL	Postural sway	Erythrocyte protoporphyrin (EP) elevation in females Increased urinary δ-aminolevulinic acid		
10 µg/dL		Inhibition of δ-aminolevulinic acid dehydratase (ALAD)	Elevated blood pressure	
5 µg/dL			↓ (???)	Elevated serum creatine (↓ creatine clearance)
0 µg/dL				

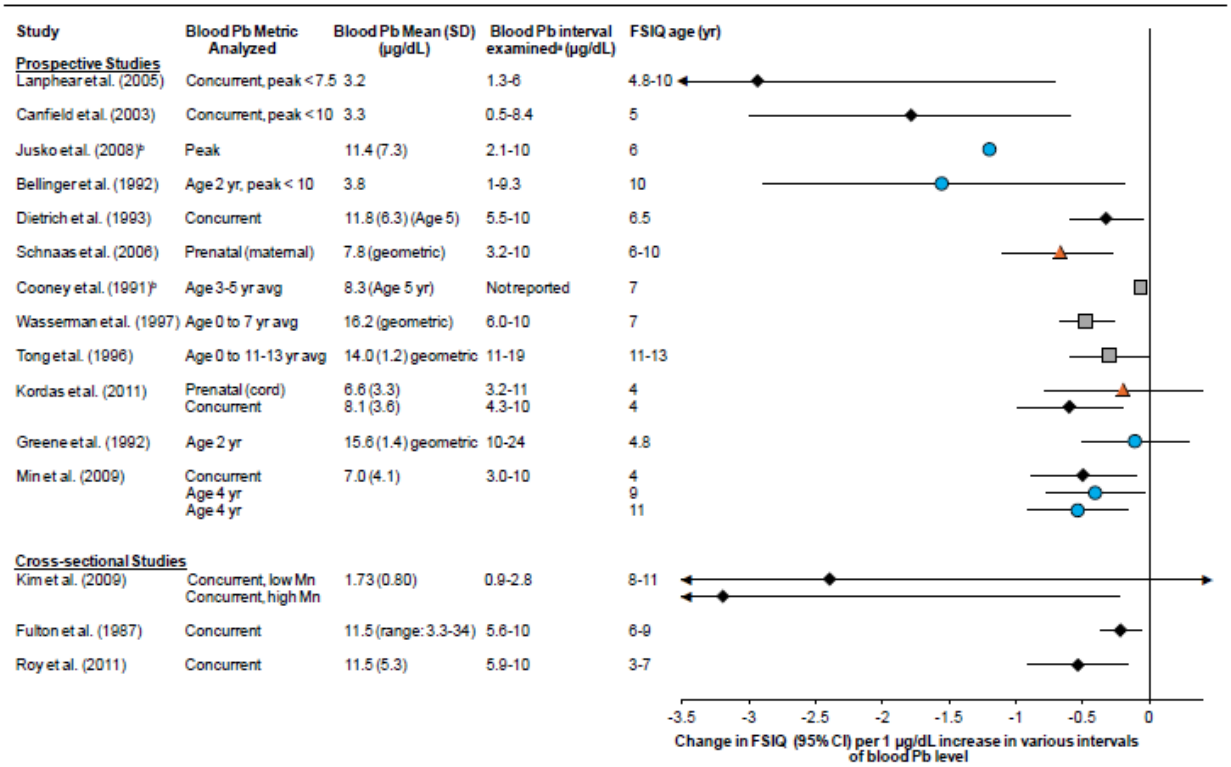
Note: Arrows depict cases where weight of overall evidence strongly substantiates likely occurrence of type of effect in association with blood-Pb concentrations in range of 5-10 µg/dL, or possibly lower, as implied by (???). Although no evident threshold has yet been clearly established for those effects, the existence of such effects at still lower blood-Pb levels cannot be ruled out based on available data.

Source: Adapted/updated from Table 1-16 of U.S. Environmental Protection Agency (1986a).

FIGURE I-13

Summary of Lowest Observed Effect Levels for Key Lead-Induced Health Effects in Adults (From (U.S. EPA 2007), Table 3-2)

In its most recent review of lead health effects, the U.S. EPA confirmed its previous conclusion regarding the cognitive decline in children as the most sensitive adverse effect associated with lead exposures. The effects as measured by a reduction in IQ from a number of studies are shown in the following figure. According to the review, the currently available evidence supports a median estimate of -1.75 IQ points for a change of 1 µg/dL blood lead to describe the neurocognitive impacts on young children (U.S. EPA 2015c).



[a]See Table 4-3 for explanation of the blood Pb level interval examined. Effect estimates were calculated for the lowest range examined in the study or the 10th percentile of blood Pb level to a blood Pb level of 10 µg/dL.
[b]Sufficient data were not available to calculate 95% CI.

Note: Mn = manganese. Results are presented for most of the cohorts examined in the literature and generally are grouped according to strength of study design, representativeness of the study population characteristics and blood Pb levels examined, and extent of consideration for potential confounding. There is not necessarily a continuum of decreasing strength across studies. Results usually are presented for the oldest age examined in cohorts. Multiple results from a cohort are grouped together. To facilitate comparisons among effect estimates across studies with different distributions of blood Pb levels and model structures (e.g., linear, log-linear), effect estimates are standardized to a 1 µg/dL increase for the lowest range of blood Pb levels examined in the study or the interval from the 10th percentile of blood Pb level to 10 µg/dL. For populations with 10th percentiles near or above 10 µg/dL, the effect estimate was calculated for the 10th to 90th percentile of blood Pb level. The percentiles are estimated using various methods and are only approximate values. Effect estimates are assumed to be linear within the blood Pb level interval evaluated. The various tests used to measure FSIQ are scored on a similar scale (approximately 40-160 FSIQ points). Black diamonds, blue circles, orange triangles, and gray squares represent effect estimates for concurrent, earlier childhood, prenatal, and lifetime average blood Pb levels, respectively. The horizontal lines associated with point estimates represent 95% confidence intervals (CI).

FIGURE I-14

Associations of Blood Pb Levels with Full-Scale IQ (FSIQ) in Children (From (U.S. EPA 2013a), Figure 4-2)

TOXIC AIR CONTAMINANTS

Toxic air contaminants are pollutants for which there generally are no ambient air quality standards. The Toxic Air Contaminant Identification and Control Act (AB 1807, Tanner, 1983) created California's first program to reduce exposures to air toxics by requiring CARB to adopt Air Toxics Control measures. Air Districts must either

enforce these measures or adopt their own equally or more stringent measures. The Air Toxics "Hot Spots" Information and Assessment Act (AB 2588, Connelly, 1987) supplements the earlier program by requiring air toxics inventories for certain facilities, notification of people's exposure to significant health risks, and facility plans to reduce these risks. Under California's Air Toxics Program, the Office of Environmental Health Hazard Assessment (OEHHA) assesses the health effects of substances that may pose a risk of adverse health effects, and CARB assesses the potential for humans to be exposed to these substances. These effects are usually an increased risk for cancer, adverse birth outcomes, or respiratory effects. After review by the state Scientific Review Panel, CARB holds a public hearing on whether to formally list substances that may pose a significant risk to public health as a Toxic Air Contaminant.

The California Air Resources Board listed diesel particulate matter as a Toxic Air Contaminant in 1989. The International Agency for Research on Cancer, an arm of the World Health Organization, classified diesel exhaust as probably carcinogenic to humans in 1989 (International Agency for Research on Cancer 1989). More recently, IARC convened an international panel of scientists to review the published literature since the initial classification regarding the carcinogenicity of diesel combustion emissions. The panel concluded that diesel exhaust is a substance that causes lung cancer in humans (International Agency for Research on Cancer 2012).

OEHHA also establishes potency factors for air toxics that are carcinogenic. The potency factors can be used to estimate the additional cancer risk from ambient levels of toxics. This estimate represents the chance of contracting cancer in an individual over a lifetime exposure to a given level of an air toxic and is usually expressed in terms of additional cancer cases per million people exposed.

For non-cancer health effects, OEHHA has developed acute and chronic Reference Exposure Levels (RELs). RELs are concentrations in the air below which adverse health effects are not likely to occur. Acute RELs refer to short-term exposures, generally of one-hour duration. Chronic RELs refer to long-term exposures of several years. OEHHA has also established eight-hour RELs for several substances. The ratio of ambient concentration to the appropriate REL can be used to calculate a Hazard Index. A Hazard Index of less than one would not be expected to result in adverse effects (Dodge et al. 2015).

SCAQMD conducted studies on the ambient concentrations and estimated the potential health risks from air toxics (South Coast Air Quality Management District 2000; South

Coast Air Quality Management District 2008; South Coast Air Quality Management District 2015). In the latest SCAQMD Multiple Air Toxics Exposure Study, MATES IV, a one-year monitoring program was undertaken at 10 sites throughout the SCAB over the time period July 2012 – June 2013 (South Coast Air Quality Management District 2015). Over 30 substances were measured, which included the toxics that contributed the most to health risks in the Basin. The results showed that the overall lifetime risk for excess cancer from a 70-year lifetime exposure to the levels of air toxics calculated from the regional model was 367 in a million. This reflects a greater than 50% reduction in exposures and risks compared to the MATES III Study that was conducted from 2004 -2006. The largest contributor to this risk was diesel particulate matter, accounting for 68% of the air toxics risk. The average measured levels were also compared to the non-cancer chronic Reference Exposure Levels (RELs), and found to be below the established RELs for the over 30 substances measured.

In 2015, OEHHA updated the calculation procedure to estimate cancer risks from air toxics exposures (Dodge et al. 2015). The revisions to the calculation methodology included accounting for higher risks attributable to early life exposures (up to age 16 years), updates to the population distribution of breathing rates by age, and a reduction in the time of household residence. In combination, these changes resulted in risk estimates in the MATES IV study to be about 2.5 times higher than the previous methodology employed in the MATES studies. The average lifetime risk for excess cancer cases is estimated to be 897 per million using the updated procedure (South Coast Air Quality Management District 2015). However, it is important to note that these results represent a more refined risk estimation methodology, not an increase in risk. Results from the MATES IV study still represent about a 50% reduction in air toxics levels and cancer risk compared to MATES III (conducted in 2004-2006).

CONCLUSION

A large body of scientific evidence shows that the adverse impacts of air pollution on human and animal health are clear. A considerable number of population-based and laboratory studies have established a link between air pollution and increased morbidity and, in some instances, premature mortality.

As the scientific methods for the study of air pollution health effects have progressed over the past decades, adverse effects have been shown to occur at lower levels of exposure. For some pollutants, no clear thresholds for effects have been demonstrated. The new findings have, in turn, led to the revision and lowering of National Ambient

Air Quality Standards which, in the judgment of the Administrator of the U.S. EPA, are necessary to protect public health. Figures I-15 and I-16 are meant to convey some of the historical context to recent revisions to the NAAQS for ozone and for particulate matter.

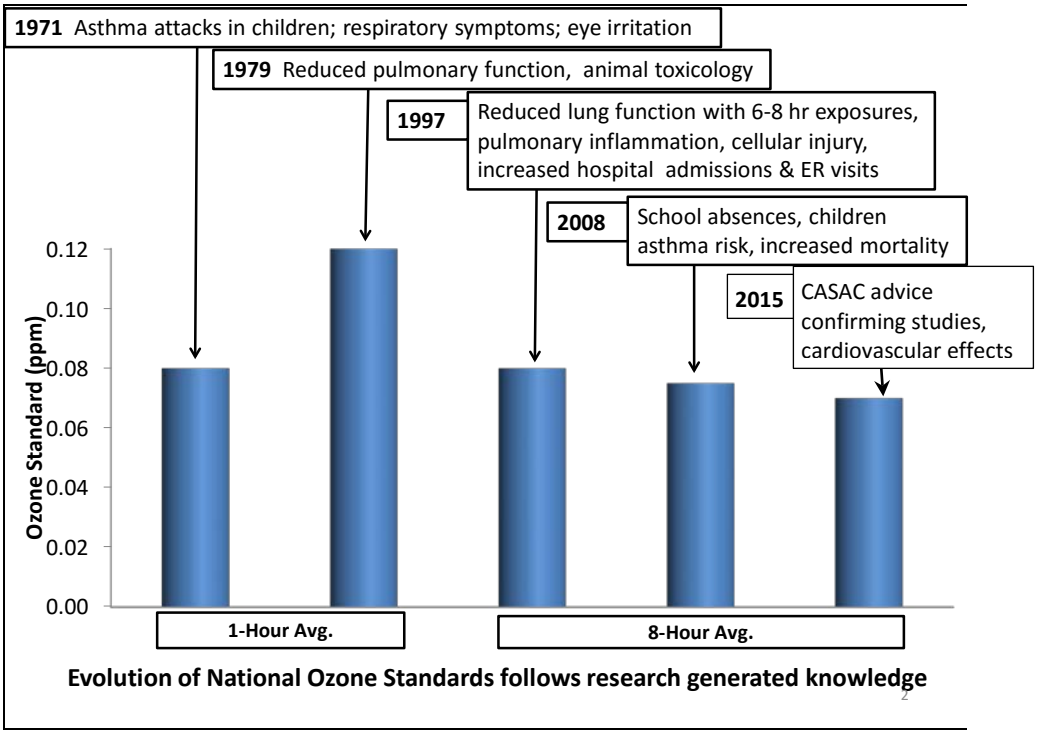


FIGURE I-15

Historical Context to Revisions of NAAQS for Ozone

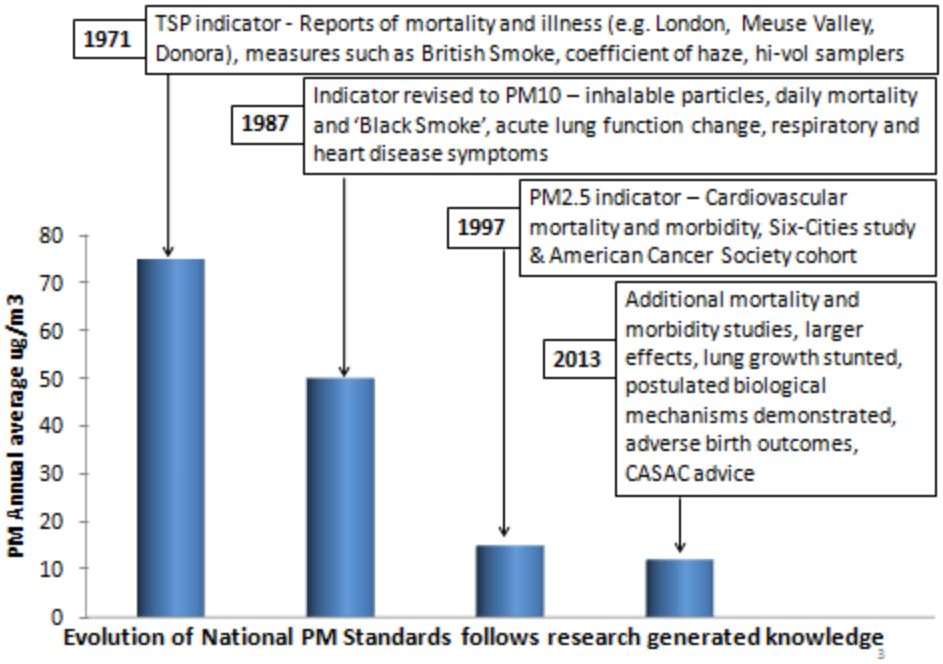


FIGURE I- 16

Historical Context to Revisions of NAAQS for PM

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DRAFT 2016 AQMP
APPENDIX I
Attachment

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OCTOBER 2015

A new compact aerosol concentrator for use in conjunction with low flow-rate continuous aerosol instrumentation
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Air Pollution and Type 2 Diabetes Prevalence, Control, and Risk Factors. Final Report.
Ying-Ying Meng, Susan Babey, Michael Jerret
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Air Pollution and Type 2 Diabetes Prevalence, Control, and Risk Factors
PI: Ying-Ying Meng, DrPH, Co-Is: Susan Babey, PhD, Michael Jerrett, PhD, Study Coordinator: Melissa Pickett, MPH, UCLA Center for Health Policy Research
Final Report submittd to BP.ACAQMD Public Benefits Oversight Committee, October 22, 2014

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