SOUTH COAST AIR QUALITY MANAGEMENT DISTRICT

Appendix I
Health Effects

South Coast AQMD

2016 AIR QUALITY MANAGEMENT PLAN

DECEMBER 2016

DRAFT FINAL 2016 AQMP
APPENDIX I

HEALTH EFFECTS

DECEMBER 2016

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ATTACHMENT
Publications from Health Related Research Projects Funded by SCAQMD

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 sections discussing the health effects of the other major pollutants. The intention of this document is to provide a brief summary of the conclusions of scientific reviews conducted by U.S. EPA and other scientific agencies, with some additional information from more recently published studies.

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. Some of these studies are discussed in this Appendix, as appropriate, although there are many other studies referenced here. The studies funded by SCAQMD also help inform the SCAQMD's work in characterizing the air pollution and its effects in our local region and the influences of sources of air pollution in the Basin.

While information on ambient air quality statistics, attainment status, spatial distribution of air pollutants, environmental justice, socioeconomic impacts, control strategies, and cost-effectiveness are important issues that may relate to health effects, these issues are not the focus of this aAppendix, and are instead discussed in detail in other chapters and appendices of the AQMP, or in the AQMP Socioeconomic Report.

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

Adverse health outcomes linked to air pollution include cardiovascular effects, premature mortality, respiratory effects, cancer, reproductive effects, neurological effects, and other health outcomes. The evidence linking these effects to air pollutants is derived from population-based observational and field studies (epidemiological), toxicological studies, 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. While the combined effects of multiple air pollutants that occur simultaneously may be important, Evidence for more than additive effects has not been strong and, the air quality standards address each criteria pollutant separately, as a practical matter, health scientists, as well as regulatory officials, usually must deal with and thus, this Aappendix is divided into sections by pollutantone 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 aAppendix.

Because the SCAB exceeds the federal standards for ozone and PM2.5, this ~~a~~Appendix focuses more attention in the discussion of these two pollutants, since the health impacts within the SCAB are potentially greater for these two pollutants compared to the health impacts of the other criteria pollutants. For the other pollutants, a brief summary of the associated health effects ~~associated with those pollutants~~ is provided.

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 2013b), and from the most recent U.S. EPA Integrated Science Assessment (ISA) 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 ~~a~~Appendix (American Thoracic Society 1996a; Brunekreef et al. 2002). More detailed citations and discussions on air pollution health effects can be found in these references.[1] Additionally, ~~This summary also draws upon~~ a supplemental literature review of mortality and morbidity impacts of PM2.5, ozone, NO₂, and SO₂ was conducted for the AQMP Socioeconomic Evaluation ~~ ~~to identify more recent studies (Industrial Economics Inc. 2016b; Industrial Economics Inc. 2016a); this health effects summary also draws upon this literature review to discuss these more recent studies, particularly those published since the most recent ISA's. 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. Studies conducted in Southern California give an important "local perspective" in understanding and evaluating the health effects of air pollution. However, ~~, although~~ studies conducted in other locations ~~do~~also provide critical information that is ~~still~~ pertinent to advancing the scientific understanding of the health effects of air pollution, including effects on our local population. As such, this summary also discusses key studies that were conducted in other locations.~~.~~

Over the decades of national reviews of outdoor air pollution and their health impacts, the U.S. EPA has developed a list of five criteria by which the strength and credibility of data can be judged. This five-tier weight-of-evidence approach provides an objective basis for assessing the breadth, specificity, and consistency of evidence concerning a particular health outcome. Table I-1 ~~The table below~~ shows the five descriptors used by the U.S. EPA for assessing causality, using a weight-of-evidence approach~~health effects~~. Within each section discussing a specific pollutant ~~Also included~~

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[1] Most of the studies referred to in this ~~A~~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.

are tables showing summaries of the U.S. EPA conclusions regarding the causality of air pollution health effects, which are the conclusions of their scientific evaluation of the research studies they have reviewed. For the criteria pollutants, the discussion in this Appendix will focus only on those categories of health effects for which the U.S. EPA has determined there is a causal or likely causal relationship with the pollutant, while other health effects may be ~~mentioned~~discussed briefly. In particular, because of the relatively long time gap since the latest U.S. EPA ISA for PM (in 2009), and because the SCAB currently exceeds the federal standards for PM2.5, some additional health endpoints that are emerging as areas of interest with regard to PM exposure are discussed briefly in this Appendix.

It is important to note that the U.S. EPA is tasked with assessing new and emerging air quality science, including health studies, as part of the process of setting the federal air quality standards. In other words, the U.S. EPA's role is to assess the causal relationships between the pollutants and the different types of health endpoints. It is SCAQMD's role to describe the public health impacts of poor air quality in our region, as well as to develop and implement an emission reduction strategy to attain the federal and state ambient air quality standards. Therefore, it is not the intention of this ~~a~~Appendix to assess whether there is or is not an effect of a specific air pollutant on any particular health endpoint, but rather to summarize the health effects and causal determinations as assessed by U.S. EPA and other scientific agencies, to discuss some recent studies published since the latest U.S. EPA reviews, to give some quantitative estimates of the health impacts of particulate matter air pollution in the South Coast Air Basin, and to present a "local perspective" by highlighting studies conducted in the South Coast Air Basin, Southern California, or California.

TABLE I-1

U.S. EPA's 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.
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 co-pollutant 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, o~~Ozone, or its reaction products, can penetrate into the gas exchange region of the deep lung. Both short-term and long-term exposures to ozone have been linked to respiratory effects. Ozone from man-made sources is formed by photochemical reactions when pollutants such as volatile organic compounds, nitrogen oxides, and carbon monoxide react with sunlight. The main sources of such ozone precursors are discussed in detail in the draft 2016 AQMP Chapter 3. Additionally, a discussion of the spatial distribution of ozone is provided in the draft 2016 AQMP Chapter 2.

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). While the federal standards must be attained within a specified time frame, the California standards do not have specific defined deadlines, but must be attained by the earliest practicable date.

The table~~s~~ below provide~~s~~ 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 U.S. EPA's Causal Determinations for Health Effects of ~~Short-Term Exposures to~~ Ozone

SHORT-TERM EXPOSURES	
~~HEALTH CATEGORY~~Health Outcome	~~CAUSAL DETERMINATION~~Causality 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
LONG-TERM EXPOSURES	
Health Outcome	Causality 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, the depth of the breaths, and the volume of air reaching the lungs, resulting in an increased amount of ozone reaching deeper into 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 (U.S. EPA 2013b).

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. For short-term ozone exposures, the U.S. EPA determined in the most recent ISA that the evidence supports a causal relationship for respiratory effects, and a likely causal relationship for cardiovascular effects and mortality.

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. 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 (forced expiratory volume in 1 second, or 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 percent%, 7 percent%, and 11 percent% 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 ozone in the range of 0.06 to 0.10 ppm ozone for 6.6 hours while engaging in intermittent moderate exercise, and found that the study participants exhibited an approximately 2 percent% reduction in lung function (FEV1) and an increase in pulmonary inflammation after exposure to ozone at the 0.06 ppm concentration.
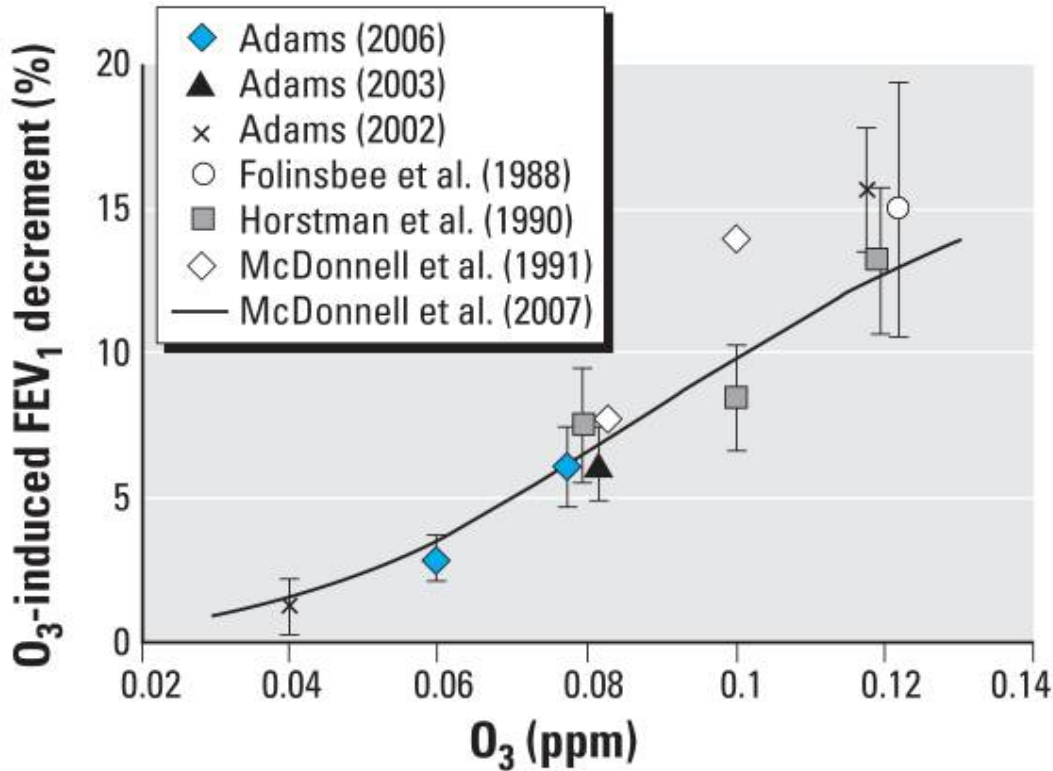
FIGURE I-1

Comparison of mean ozone-induced decrements in lung function following 6.6 hours of ozone exposure. Error bars represent are the standard error. McDonnell et al. (2007) was a summary of results from several studies, and is represented by the line in the graph. (From: (Brown et al. 2008))

Some changes in lung function responses (volume and airway resistance changes) observed after study participants were exposed to a single exposure to ozone only once exhibit attenuatedion responses or a reduction in magnitude of responses when with repeated exposures are repeated, although there were a range of individual human responses observed, including some non-responders (Linn et al. 1988). Although it has been argued that the observed shift in response is evidence of a probable development of adaptationtolerance 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 attenuationadaptation. 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 adaptationtoleration is that after several days or weeks without ozone exposures, the responsiveness (in terms of lung function as well as symptoms) returns, which is evidence that any tolerance developed is relatively short-lived (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 . 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.

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 (TNF-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 .

In addition to controlled laboratory conditions, epidemiological 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 2013 review ISA indicatesd that most studies found reductions in lung function (FEV$_1$) in the range of approximately <1 to 2 percent% 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 percent%) were found in children with asthma who had respiratory infections or were using corticosteroid medication.

Epidemiologic studies have found that Iincreases in short-term ozone levels are associated with impacts on children's respiratory health, including increases in respiratory symptoms in children with

asthma, and increased numbers of absences from school. Studies conducted in various cities in the U.S. and in other countries have reported increased respiratory symptoms among children with asthma, including wheeze, cough, difficulty breathing, and chest symptoms/tightness (U.S. EPA 2013b). 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 short-term increases in ambient ozone levels. An increase of 20 ppb (0.02 ppm) ozone was associated with a 63 percent% increase in illness-related absence rates (95% confidence interval = 18%-124%) and an 83 percent% increase in respiratory illnesses (95% confidence interval=4%-222%) (Gilliland et al. 2001). A small panel study of Hispanic children with asthma living in the Huntington Park neighborhood of Los Angeles, California reported that a 10.8 ppb increase in ozone averaged over 8 hours nearly doubled the odds of having asthma symptoms that interfered with daily activities (Delfino et al. 2003). Despite thisthese studiesy, and some others linking ozone exposures with school absences, the U.S. EPA concluded that only limited evidence is currently available linking these ozone exposures to respiratory-related school absences (U.S. EPA 2013b).

Numerous studies have found associations of short-term ozone levels and hospital admissions and emergency department admissions for respiratory-related conditions, and the U.S. EPA concluded in the latest ISA that the most recent epidemiological studies conducted in both single cities and multiple cities continue to provide evidence supporting a causal relationship between short-term ozone exposures and respiratory effects (U.S. EPA 2013b). The studies generally found stronger associations for asthma and COPD in the warm season or in the summer months, compared to the cold season, and also provided evidence that children are at greatest risk of ozone-related respiratory health effects. A Canadian multi-city study reported that a 20 ppb increase in 24-hour ozone concentrations increased emergency department visits for asthma 2 days later by 3.5% (95% confidence interval: 0.33%, 6.8%) {Stieb, 2009 #364}. The average ozone concentrations in this Canadian study was 18.4 ppb averaged over 24 hours, suggesting that ozone can exert effects even at relatively low ambient levels. A study of children aged 5-17 years in Atlanta, Georgia reported a 6.4% increase (95% confidence interval 3.2% 9.6%) associated with a 30 ppb increase in the maximum ozone concentration averaged over 8 hours {Strickland, 2010 #365}. Strickland et al. used a population-weighting technique to combine pollutant measurements across several monitors in the city, rather than using a single centrally-located monitor. Additionally, the authors controlled for the potential effects of other pollutants, and reported that the findings for ozone remained largely the same. The authors reported that the effects of ozone exposures were observed at concentrations as low as 30 ppb.Several of these studies reviewed in the ISA had average ozone concentrations well below 60 ppb averaged over 8 hours and still reported associations with respiratory outcomes. One study of asthma emergency department visits reported ozone effects at concentrations as low as 30 ppb (Strickland et al. 2010). 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 morbidityhospital admissions or emergency department visits. This figure illustrates the associations found between ambient ozone exposure and key respiratory outcomes (asthma, COPD and pneumonia), and shows the stronger effects with summertime ozone exposures. AdditionallyRecently, Aa recent study in California reported that short-term ozone exposures were associated with emergency department visits for asthma, acute respiratory infections, pneumonia, COPD, and upper respiratory tract infections, with more consistent associations during the warm season (Malig et al. 2016). This California study provides additional supporting evidence for ozone-related respiratory effects.

The potential cardiovascular effects of short-term ozone exposure have been studied in toxicological, human exposure, and epidemiological studies. Controlled human exposure studies have found that ozone exposures produce changes in heart function (as measured by heart rate variability) and increases in biomarkers in the blood for systemic inflammation and oxidative stress. The limited number of toxicological studies on this topic provide evidence of cardiovascular effects. The effects observed include increased heart rate variability, arrhythmias, vascular disease, and inflammation and oxidative stress leading to atherosclerosis, which can lead to tissue damage due to ischemia and reperfusion (i.e. having the blood supply cut off and then restored to the tissues) (U.S. EPA 2013b). The controlled human exposure and toxicological studies provide evidence of cardiovascular effects of ozone, and some plausible mechanisms for these effects. Epidemiological studies, including some recent multi-city studies show relatively consistent associations between short-term ozone exposures and cardiovascular mortality (these studies are discussed further below). However, epidemiological studies do not provide consistent evidence of cardiovascular morbidity with short-term ozone exposures. Studies conducted in the Los Angeles area or in California also do not provide consistent evidence of short-term ozone effects on cardiovascular morbidity. A study of elderly non-smokers in the Los Angeles area with a history of heart disease found no associations between ozone exposure and blood pressure nor ST-segment depression, a measure of cardiac ischemia (Delfino et al. 2010; Delfino et al. 2011).

 A Los Angeles-based study of cardiovascular hospital admissions did not find increased risk with ozone exposures (Linn et al. 2000). However, Aa biomarker study of students at UC Berkeley who spent their summer vacation in either the Los Angeles or San Francisco Bay Area found that ozone exposures over a period of 2 weeks or 1 month were associated with increases in a biomarker of lipid peroxidation, but no association was found for a biomarker of antioxidant capacity (Chen et al. 2007). Lipid peroxidation biomarkers is are an indicator of oxidative stress, which may be triggered by pulmonary inflammation caused by ozone exposure. Given the strong evidence of cardiovascular morbidity from experimental studies and the consistent positive associations reported in epidemiological studies of cardiovascular mortality, but the lack of consistent evidence from epidemiological studies of cardiovascular morbidity, the U.S. EPA determined that there is a "likely causal relationship" between short-term ozone exposures and cardiovascular effects (U.S. EPA 2013b).

~~(LA) In a study of ozone effects on blood pressure among elderly non-smokers with a history of heart disease, no association was found between ozone exposure and blood pressure {Delfino, 2010 #370}~~

For mortality effects, ~~(LA) No association among elderly non-smokers with a history of heart disease between ozone exposure and ST-segment depression, a measure of cardiac ischemia {Delfino, 2011 #293}.~~

~~T~~the U.S. EPA 2013 ISA concluded that there was a "likely causal relationship" ~~between~~for short-term ozone exposures ~~and mortality~~. This determination is supported by ~~N~~numerous studies have found positive associations between short-term increases in ozone levels and excess risk of mortality from all non-accidental causes, ~~and~~cardiovascular causes, and respiratory causes (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). ~~Recent s~~Studies conducted across multiple cities in the U.S. Canada, ~~and~~Europe and Asia reported increased cardiovascular and respiratory mortality risks ~~and~~with increased short-term ozone exposures, and several studies additionally reported increased mortality risk for summer season ozone exposures (Katsouyanni et al. 2009; Samoli et al. 2009; Stafoggia et al. 2010; Wong et al. 2010). Some studies have also demonstrated that ~~While there is substantial evidence supporting a causal relationship between short-term ozone exposures and respiratory morbidity, the evidence linking such exposures to mortality from respiratory causes is more mixed. T~~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~~,~~ although there is some variability across studies with regard to the sensitivity of the ozone associations to adjustment for PM (Bell et al. 2004; Huang et al. 2005; Katsouyanni et al. 2009; Stafoggia et al. 2010). With regard to respiratory effects, ~~Ww~~while ~~the~~there ~~re is~~substantial evidence supporting a causal relationship between short-term ozone exposures and respiratory morbidity~~,~~ provides strong support for the recent ~~the~~ evidence from epidemiological studies linking such exposures to respiratory mortality. ~~With regard to~~For cardiovascular effects, while there is strong evidence linking cardiovascular mortality with short-term ozone exposures, the ~~evidence from~~ epidemiological studies of non-fatal outcomes do not provide consistent evidence for a coherent mechanism linking ozone exposures to cardiovascular mortality ~~from respiratory causes is more mixed despite recent multicity studies finding consistent positive associations for exposures during the summer months~~ (U.S. EPA 2013b). ~~The likely causal relationship between short-term ozone exposures and mortality is primarily based on the strength of evidence from studies of cardiovascular mortality.~~

Examples of studies showing the relative change in mortality risks for all-year and summer-only analyses are shown in Figure I-3.
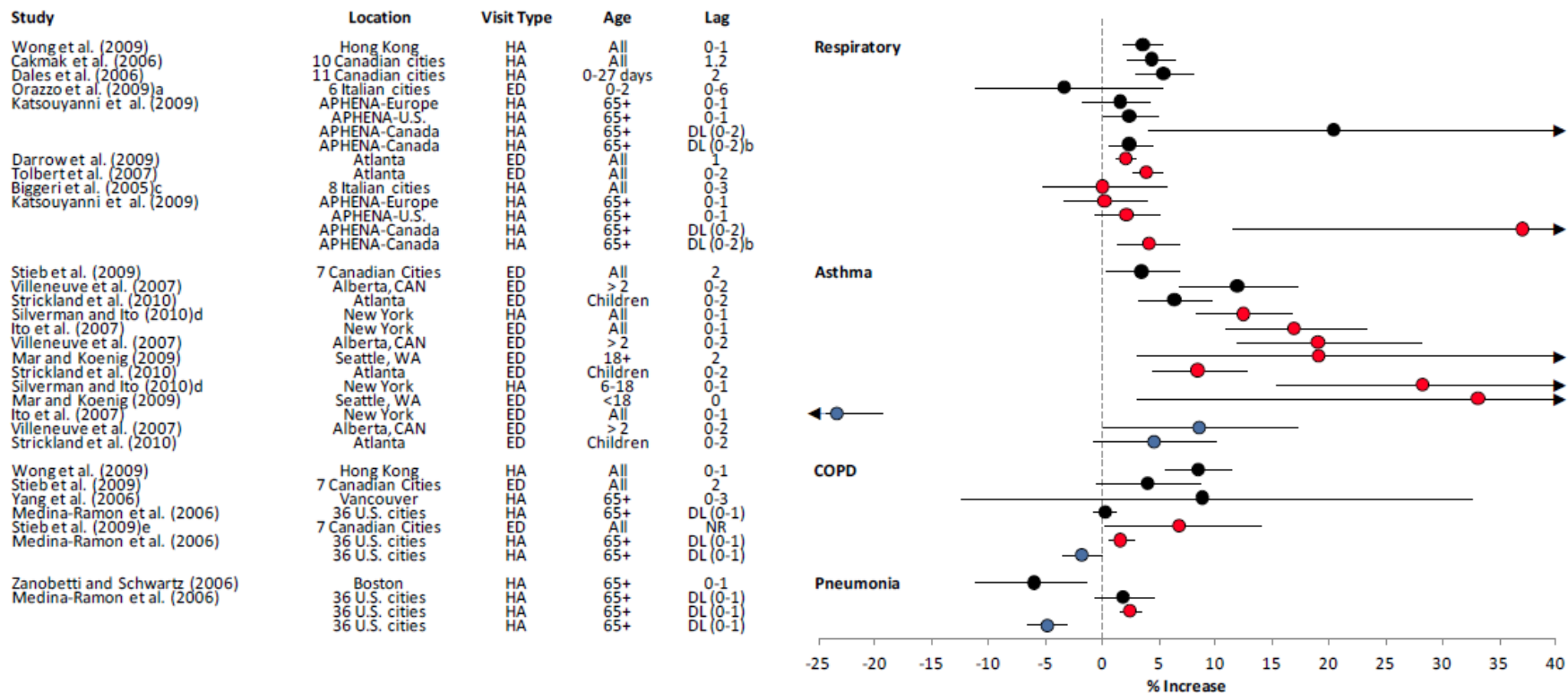
Note: Effect estimates are for a 20 ppb increase in 24-hour; 30 ppb increase in 8-hour max; and 40 ppb increase in 1-hour max O$_3$ concentrations. HA=hospital admission; ED=emergency department. Black=All-year analysis; Red=Summer only analysis; Blue=Winter only analysis. (From (U.S. EPA 2013b) Figure 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). 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).
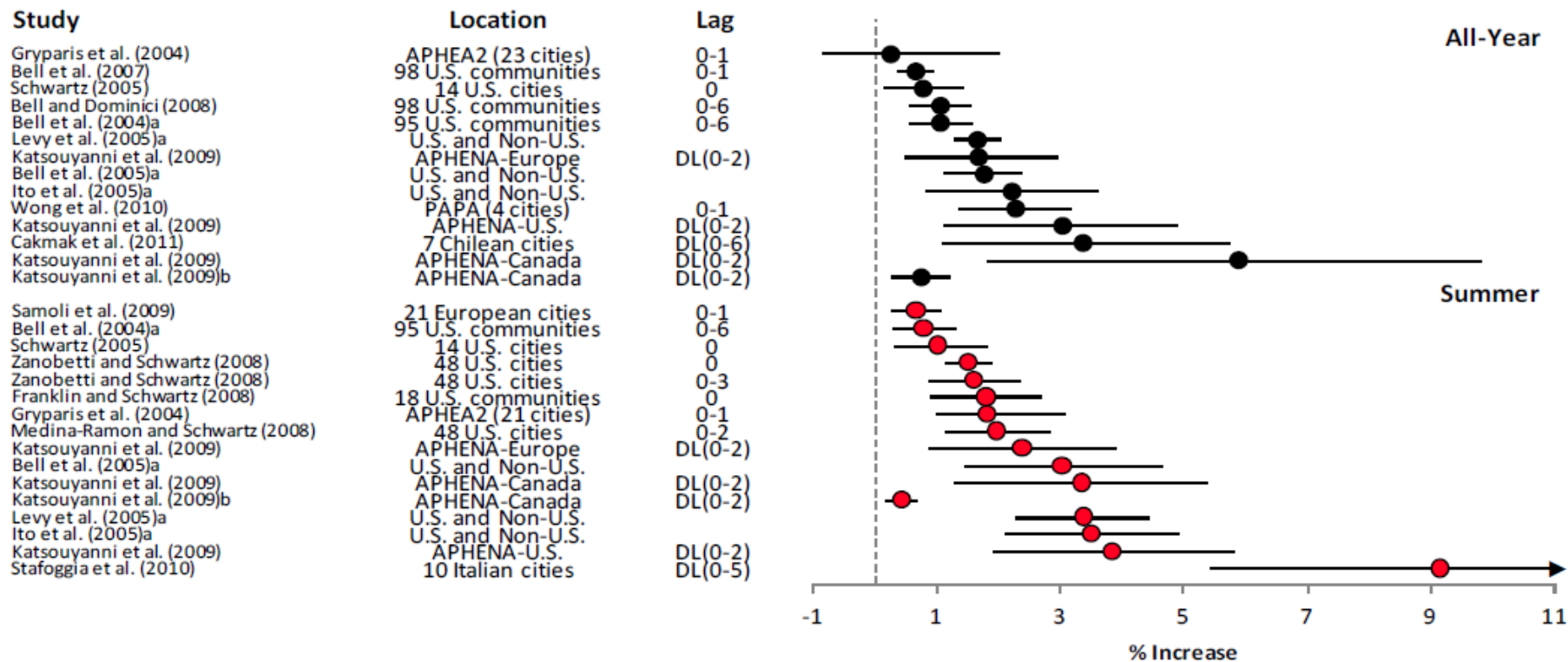
Note: Effect estimates are for a 40 ppb increase in 1-hr max, 30 ppb increase in 8-hr max, and 20 ppb increase in 24-hr average O_3 concentrations. (From (U.S. EPA 2013b) Figure 6-27)

FIGURE I-3

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

Long-Term Exposure Effects of Ozone

~~Results of epidemiology studies support the relationship between ozone exposure and respiratory effects, and t~~The U.S. EPA 2013 ISA for Ozone concluded that there was a likely causal relationship between long-term ozone exposure and respiratory effects (U.S. EPA 2013b). Evidence supporting this determination comes from epidemiological and ~~studies and experimental~~ toxicological studies ~~in humans and animals~~, particularly studies of asthma and related symptoms, asthma-related hospital admissions, lung function, lung inflammation and oxidative stress. Other health effects of long-term ozone exposure were determined to have "suggestive" or "inadequate" evidence of causality, although the few studies of respiratory mortality provide support to the respiratory health effects of ozone.

~~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).~~

The Adventist Health and Smog Study (AHSMOG) and Children's Health Study cohorts are two large long-term studies conducted in California that examined several aspects of long-term ozone effects in adults and children, respectively. Several of these studies focused on asthma development and exacerbation. The AHSMOG study included adult, non-smoking, non-Hispanic white Seventh Day Adventists living in California. The 10-year follow-up AHSMOG study reported that a 10 ppb increase in annual mean ozone exposures increased the risk of asthma development in males by three-fold (relative risk 3.12, 95 percent~~%~~ confidence interval: 1.16, 5.85), but no effect was seen among females (relative risk 0.94, 95 percent~~%~~ confidence interval: 0.65, 1.34) (Greer et al. 1993). The 15-year follow-up AHSMOG study used an ozone metric focusing on 8-hour average exposures, and reported that a 10 ppb increase was associated with a 30 percent~~%~~ increased risk of developing asthma in males (relative risk 1.31, 95 percent~~%~~ confidence interval: 1.01, 1.71), and these effects persisted even after accounting for other pollutants (McDonnell et al. 1999). The latter study also found no effect in females, although this may reflect a greater potential for misclassification of air pollution exposure in females compared to males, due to different time-activity patterns resulting in greater time spent outdoors among males (U.S. EPA 2013b)~~{McDonnell, 1999 #373}~~. ~~A publication from the Children's Health Study focused on children and outdoor exercise.~~ In the Children's Health Study, among children living in 12 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). The high ozone communities had a 4-year mean daytime ozone concentration of 59.6 ppb, compared to 40.0 ppb for the low-ozone communities. 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). These studies did not examine whether genetic factors may have played a role in making some people more susceptible than others to the respiratory effects of ozone exposure. Some analyses from the Children's Health Study identified specific genetic variants that, when combined with ambient ozone exposure, either increase or decrease the risk of developing asthma (Islam et al. 2008; Islam et al. 2009; Salam et al. 2009). These genetic variants are involved with antioxidant and/or anti-inflammatory pathways, and are likely involved in key elements of asthma development (U.S. EPA 2013b).

Other studies examined the impact of long-term ozone exposures and respiratory symptoms, particularly among asthmatics. ~~Another study from the CHS found that asthmatic children with a particular genetic variant that reduces expression of the cytokine TNF-α (as part of an inflammatory response) had reduced risk of bronchitic symptoms for children in low-ozone communities, but not for children in high-ozone communities {Lee, 2009 #377}.~~ Studies have linked long-term ozone exposures to increased risk of having poorly-controlled asthma~~These genetic variants are involved with antioxidant and/or anti-inflammatory pathways, and are likely involved in key elements of asthma development {U.S. EPA, 2013 #159}.~~, increased asthma symptoms, and respiratory-related school absences (Gilliland et al. 2001; Akinbami et al. 2010; Jacquemin et al. 2012). An analysis from the CHS found no association between long-term ozone exposures and chronic lower respiratory tract symptoms, and another found an increased risk of bronchitic symptoms within a community, although the association was reduced when accounting for other pollutants (McConnell et al. 1999; McConnell et al. 2003). However, two studies from the CHS demonstrated gene-environment interactions for genes that are involved in inflammation or antioxidant pathways. One study found that asthmatic children with a particular genetic variant that reduces expression of the cytokine TNF-α (as part of an inflammatory response) had reduced risk of bronchitic symptoms for children in low-ozone communities, but not for children in high-ozone communities (Lee et al. 2009). A second study found that a particular genetic variant reduced the risk of respiratory-related school absences among children living in communities with high levels of ozone (defined in this study as being above the median value of 46.9 ppb) (Wenten et al. 2009).

Results of epidemiologic studies of hospital admissions and emergency department visits support the relationship between ozone exposure and respiratory effects. In a 2007 study conducted in Southern California, an increased risk of having poorly-controlled asthma was associated with living in areas above the 90th percentile ozone level (28.7 ppb, annual average) among men and elderly individuals (Meng et al. 2007). A study in the South Coast Air Basin found that ozone was associated with increased hospital discharges for asthma among children (Moore et al. 2008). Another study in the South Coast Air Basin looked at infants hospitalized for bronchiolitis. This study found a reduced risk of infant bronchiolitis hospitalization with increased ozone exposure, although there was no association for ozone when accounting for the effect of PM2.5, which was positively associated with

this respiratory outcome (Karr et al. 2007). A study of people with asthma was conducted in the San Joaquin Valley of California, and found that a 10 ppb increase in ozone exposures averaged over one year increased the odds of asthma-related hospital admissions and emergency department visits by approximately 50 percent%, and the odds of asthma symptoms among adults by about 40 percent% (Meng et al. 2010). Studies conducted in other locations have also reported increases in asthma hospitalizations (U.S. EPA 2013b).

Some animal studies show results that indicate possible chronic effects including functional and structural changes of the lung. However, although due to morphological, developmental, and immunological differences make , it is difficult to apply these results to humans experiencing ambient exposures. These changes observed in airway responsiveness provide support for the long-term effects of ozone in asthma development or exacerbation 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). However, epidemiologic studies examining long-term ozone exposures and lung function deficits have reported mixed results. For example, an analysis of the first CHS cohort found that PM2.5 and NO$_2$ exposures were associated with decreased lung function, but did not find an association for ozone (Gauderman et al. 2004). 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.

Unlike short-term ozone exposures, there is limited evidence linking long-term ozoneA exposures with mortality. A large study based on the American Cancer Society Cancer Prevention Study II (CPS-II) cohort included 96 metropolitan statistical areas in the U.S., and reported that a 10 ppb increase in daily maximum 1-hour ozone concentrations averaged between April and September (warm season) was associated with a relative risk of 1.040 (95 percent% confidence interval: 1.010, 1.067) for respiratory deaths, but no association with cardiovascular deaths (Jerrett et al. 2009). A U.S. study of Medicare enrollees reported increased risk of mortality with higher ozone exposures averaged over the warm season, among patients who had previously been hospitalized for congestive heart failure, myocardial infarction, COPD and diabetes (Zanobetti et al. 2011). A recent large-scale study found increased risk of all-cause, cardiovascular, and respiratory mortality with long-term 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). While the U.S. EPA determination in the latest ISA was that the evidence was suggestive of long-term ozone

exposure causing mortality, the studies of respiratory mortality support the evidence for the respiratory effects of ozone exposure, for which U.S. EPA has concluded there is a causal relationship.

For non-respiratory health endpoints, the U.S. EPA causal determinations were "suggestive of a causal relationship" (for cardiovascular, reproductive and developmental, central nervous system and mortality effects) or "inadequate to infer a causal relationship" (for cancer). Some studies conducted in California have examined reproductive or developmental effects, including birth defects, low birth weight or birth weight reductions, stillbirth and autism (Ritz et al. 2002; Ritz et al. 2007; Morello-Frosch et al. 2010; Becerra et al. 2013; Mobasher et al. 2013; Trasande et al. 2013; Laurent et al. 2014; Green et al. 2015; Symanski et al. 2016). Other recent studies have examined cardiovascular effects (Koken et al. 2003; Ensor et al. 2013; Rodopoulou et al. 2014). While many of these studies have reported associations with ambient ozone levels, the latestmost recent causalU.S. EPA determination in 2013 was that the evidence was suggestive of a causal determination, but did not yet rise to a higher level.

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 NO₂ 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 NOₓ 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 SO₂ 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 most recent ISA for review of ozone in 2013 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, certain lower socioeconomic status, variations in genes related to oxidative metabolism or inflammation, 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, a person's gendersex, socioeconomic status, and obesity (U.S. EPA 2013b). Some other factors that could affect sensitivity to ozone have also been studied; Hhowever, further there was inadequate evidence to conclude whether these were risk factors for ozone sensitivity is needed. The table below summarizes the evidence for factors affecting sensitivity to ozone from the 2013 ISA for ozone.

TABLE I-3

Summary of Evidence for Potential Increased Susceptibility to Ozone-Related Health Effects

Evidence Classification	Potential At Risk Factor
Adequate evidence	Genetic factors Asthma Children Older adults Diet Outdoor worker
Suggestive evidence	Sex SES Obesity
Inadequate evidence	Influenza/infection COPD Cardiovascular disease Diabetes Hyperthyroidism Race/ethnicity Smoking Air conditioning use
Evidence of no effect	--

From (U.S. EPA 2013b) Table 8-6

As previously mentioned, one group that has been recognized as being particularly sensitive to the effects of ozone is young children with asthma, because their lungs are still developing, their potential for increased exposure due to time spent exercising outdoors, and their high ventilation rates relative to body weight (U.S. EPA 2013b). Some factors that may contribute to the increased sensitivity among people with asthma include having an altered innate immune function and factors that decrease their antioxidant defenses (Alexis et al. 2014). Ozone creates secondary oxidation

products that are electrophilic, and certain genetic factors influence a person's ability to metabolize these electrophiles, which can affect respiratory function (U.S. EPA 2013b). Asthma exacerbations are more prevalent and severe in young boys than in girls, but there evidence on whether boys are more susceptible than girls to the effects of air pollution on asthma symptoms is not consistent (Guarnieri et al. 2014).

Summary – Ozone Health Effects

In summary, outdoor ozone exposures have been associated with a range of negative human health effects. The strongest evidence for negative health impacts are on the respiratory system, and are measured by decreased lung function performance and increased cell injury. In addition, the 2013 ISA also concluded that there was a likely causal relationship between short-term ozone exposures and cardiovascular effects (such as changes in heart function, and increased systemic inflammation and oxidative stress) as well as respiratory mortality. 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). adverse effects associated with ozone exposures have been well documented, with strong evidence supporting a link to respiratory effects.

The previous U.S. EPA review of ozone in the 2006 Air Quality Control riteria Document (AQCD) had already concluded that there was clear, consistent evidence that acute ozone exposure is causally associated with respiratory effects (U.S. EPA 2006). Additionally, the 2006 AQCD for ozone concluded that the evidence was highly suggestive of ozone causing mortality, but that there was limited evidence for ozone causing cardiovascular effects. In the 2013 ISA, the U.S. EPA cited that Several lines of evidence provide support for the respiratory effects of ozone, including human exposure studies, epidemiology and toxicology, which led to the conclusion and the U.S. EPA concluded in the 2013 ISA that there was a causal relationship with short-term ozone exposures, and a likely causal relationship with long-term ozone exposures. In humans, respiratory effects were detected in laboratory studies at 0.06 ppm ozone concentrations, and in epidemiological studies with average ozone concentrations as low as 0.03 ppm (Strickland et al. 2010; Kim et al. 2011). Some populations are more sensitive to the health effects of ozone than others, including elderly persons, children, outdoor workers and persons with asthma. Key respiratory effects linked to ozone include decreased lung function, increased inflammation, and increased asthma symptoms. In addition, the 2013 ISA also concluded that there was a likely causal relationship between short-term ozone exposures have also been linked to and cardiovascular effects (, such as changes in heart function, and increased systemic inflammation and oxidative stress) as well as respiratory mortality. Ozone effects have been observed

PARTICULATE MATTER

Airborne particulates are a complex group of pollutants that vary in physical, chemical, and biological dimensions. Physically, particles can vary by size, surface area and roughness, shape, and mass. Chemically, they vary by chemical composition. Biologically, they can vary by toxicity. In addition,

particles vary by source, and can come from anthropogenic (man-made, such as from combustion of fuels, or frictional abrasion) or "natural" (plants – for example, pollens and spores) origins. ~~source, size, and composition, and toxicity, 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 composition of particulate matter can vary across sub-regions, and a description of the spatial differences in PM composition can be found in the draft 2016 AQMP Chapter 2 and Appendix II.

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 focus on ~~cover~~ particles sized 10 μm (micrometers) aerodynamic diameter and smaller. These can be inhaled ~~through the upper airways~~ and deposited throughout the upper and ~~in the~~ lower respiratory system, depositing in both airways and gas-~~-~~exchange areas of ~~tissues in~~ the lung. These particles are referred to as PM10. U.S. EPA initially promulgated ambient air quality standards for PM10 of 150 μg/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.

As more health research data has become available, concerns have centered on smaller and smaller particles. ~~In more recent years, a~~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. In 2002, ~~T~~the California Air Resources Board adopted an air quality standard for PM2.5 ~~in 2002~~ at a level of 12 μg/m^3-~~,~~ in the form of an annual average.

Since that time, ~~numerous~~ additional 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)~~, with an attainment year of 2025.~~- This federal standard is set at same level as the current California PM2.5 annual standard, although the California standard does not have a specified attainment date. In 2014, the U.S. EPA announced it is preparing an ISA as part of the review of the federal PM standards (the process is described briefly in the draft AQMP Chapter 8). The draft AQMP Chapter 2 and Appendix II provide additional information about how PM levels in the South Coast Air Basin compare to the federal and state standards.

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, although a PM10 standard remains in effect. These conclusions are depicted in the following tables.

TABLE I-4

Summary of U.S. EPA's Causal Determinations ~~of~~ for Health Effects 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)

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.

TABLE I-5

Summary of U.S. EPA's Causal Determinations ~~of~~ for Health Effects 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)

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 (U.S. EPA 2009; Lu et al. 2015; Shah et al. 2015; Cai et al. 2016), although there are some studies that show no effect for the specific exposures and outcomes evaluated (Milojevic et al. 2014; Wang et al. 2015; Zu et al. 2016). While there were some of these studies were conducted in California, the importance of assessing results from studies from many different locations around the world should not be understated. The repeatability and consistency of results across many locations strengthens the weight of evidence in the determination of causality.

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 preexistingent 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 percent% 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 percent% 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 reported in the study 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). After the study was published, it was discovered that some of the study analyses had been performed with incorrect default values. ~~When the investigators re-analyzed the data using revised settings for the data, the size of the effect diminished, but the results remained largely the same~~ The strong positive association between acute PM10 exposure and mortality remained, both upon reanalysis using revised software and using alternative modeling approaches (Dominici et al. 2002; 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 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/m³ 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 percent~~%~~ for all-cause mortality and 0.38 percent~~%~~ 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 percent~~%~~ 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 percent~~%~~ per 10 µg/m^3, and for respiratory mortality estimates range from 1.01 to 2.2 percent~~%~~ per 10 µg/m^3 24-hour PM2.5 (U.S. EPA 2009). Figure I-4 shows a summary of ~~recent~~ U.S. and Canadian studies of mortality and short-term PM2.5 exposures, which shows that ~~.~~ the most consistent positive associations were seen with cardiovascular and all-cause deaths. Positive associations for respiratory deaths were also seen in several of these studies, although the precision of ~~amount of uncertainty in~~ the estimates for respiratory deaths was ~~larger~~ lower relative to that of all-cause or cardiovascular deaths.

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).
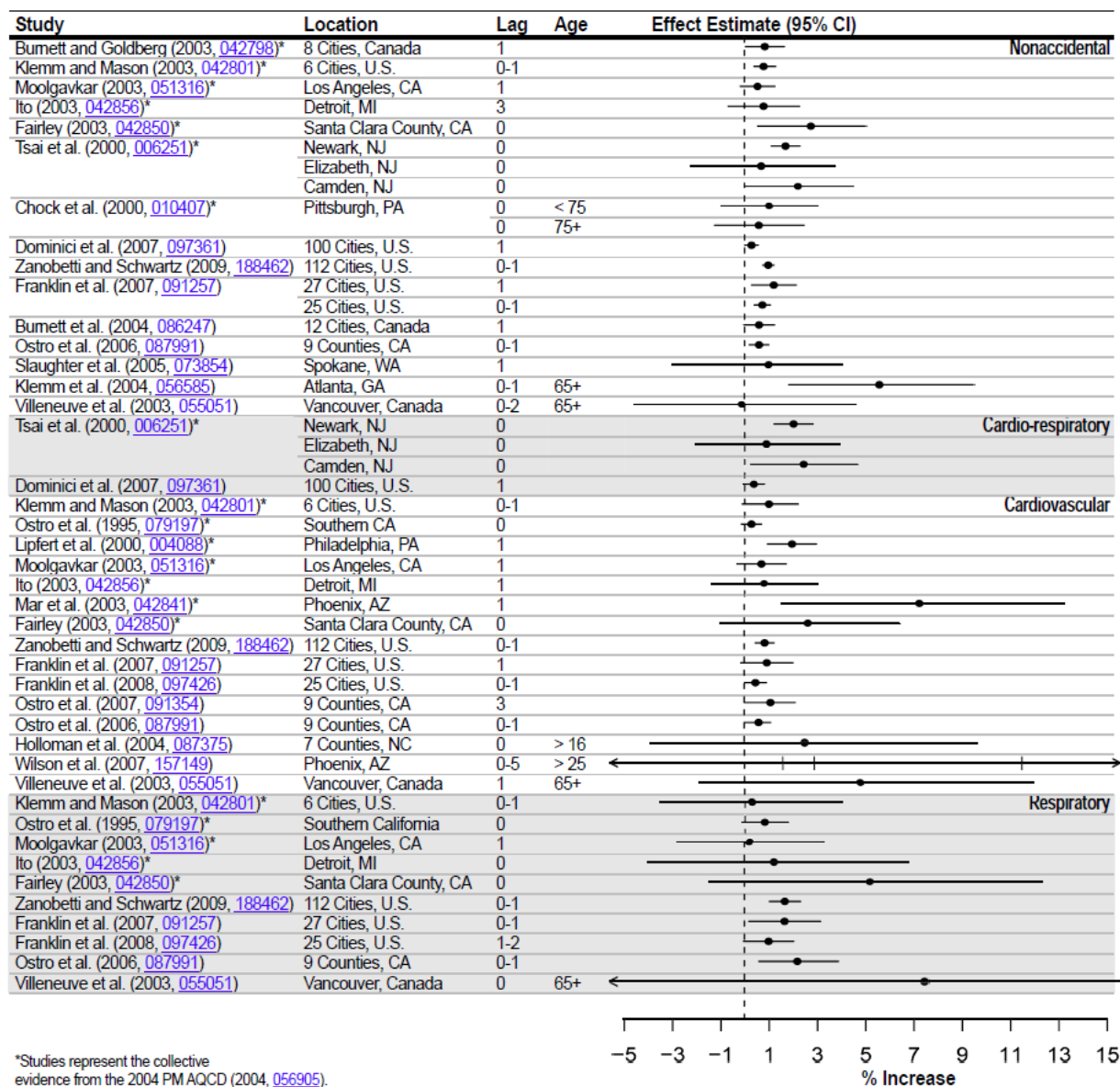

FIGURE I-4

Summary of Non-accidental All-Cause and Cause-Specific Mortality per 10 µg/m3 Increase in PM2.5 Short-term Exposures, for U.S.- and Canadian-based studies

(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 in understanding the ~~is the~~ relative importance of "fine" PM (PM2.5) and "coarse" PM (PM10-2.5) is the relative lack ~~paucity~~ of direct measurements of PM10-2.5 ~~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. Consistent positive associations are seen, particularly for cardiovascular and nonaccidental all-cause mortality, with varying degrees of precision across the different studies.

Study	Location	Lag	Age**	Effect Estimate (95% CI)	
Klemm et al. (2003, 042801)*	6 Cities, U.S.	0-1			Nonaccidental
Burnett and Goldberg (2003, 042798)*	8 Cities, Canada	1			
Ito (2003, 042856)*	Detroit, MI	1			
Fairley (2003, 042850)*	Santa Clara County, CA	0			
Chock et al. (2000, 010407)*	Pittsburgh, PA	0	<75		
		0	75+		
Zanobetti and Schwartz (2009, 188462)	47 Cities, U.S.	0-1			
Burnett et al. (2004, 086247)	12 Cities, Canada	1			
Klemm et al. (2004, 056585)	Atlanta, GA	0-1	65+		
Villeneuve et al. (2003, 055051)	Vancouver, Can	0			
Lipfert et al. (2000, 004088)*	Philadelphia, PA	1			Cardiovascular
Ito (2003, 042856)*	Detroit, MI	1			
Mar et al. (2003, 042841) *	Phoenix, AZ	0			
Fairley (2003, 042850)*	Santa Clara County, CA	0			
Ostro et al. (2003, 042824)*	Coachella Valley, CA	0			
Zanobetti and Schwartz (2009, 188462)	47 Cities, U.S.	0-1			
Wilson et al. (2007, 157149)	Phoenix, AZ	0-5	>25		
Villeneuve et al. (2003, 055051)	Vancouver, Can	0	65+		
Ito (2003, 042856)*	Detroit, MI	2			Respiratory
Fairley (2003, 042850)*	Santa Clara County, CA	0			
Zanobetti and Schwartz (2009, 188462)	47 Cities, U.S.	0-1			
Villeneuve et al. (2003, 055051)	Vancouver, Canada	0	65+		

* Studies represent the collective evidence from the 2004 PM AQCD (2004, 056905).
**If age not specified, study included all ages.

−5 −3 −1 1 3 5 7 9 11 13 15
% Increase

FIGURE I-5

Summary of Percent Increase in Total (Nonaccidental) and Cause-Specific Mortality Per 10 µg/m3 Increase in PM10-2.5 Short-term Exposure (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 for these various morbidities are generally higher than the estimates for mortality. ~~The~~ Observed effects have been ~~are~~ associated with ~~measures of both~~ PM10, ~~and~~ PM2.5 and PM10-2.5. ~~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 percent for cardiovascular diseases, a range of 1.46 – 2.88 percent increase for COPD, and a range of 1.31 – 2.86 percent 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, NO_x, 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 percent 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 percent 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). A study in cells using ambient air samples in communities near railyards in the South Coast Air Basin have found also shown that the particlePM2.5 phase of ambient air pollution contains prooxidant components, primarily metals, which can trigger an inflammatory response in the cells (Eiguren-Fernandez et al. 2015; Cho 2016). The same study also noted that vapor phase pollutants, which contain most of the electrophiles, including volatile organic compounds may trigger a different biological n adaptationadaptive response in the cells, which would suppressing the inflammatory responses and could result in a reduced ability to respondfight offto infections.

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.

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. This section provides a discussion of long-term particulate matter exposures and several key health endpoints.

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 survey included several measures of smoking and exposure to second-hand smoke, which were included in the statistical models to account for the potential confounding effects of smoking. 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 percent~~%~~ increase in total mortality, a 6 percent~~%~~ increase in cardiopulmonary mortality, and an 8 percent~~%~~ 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 µg/m³ 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 is a large prospective cohort study of adults in six U.S. cities, and began in the year 1974. The original analysis and a subsequent reanalysis found positive associations between ~~evaluated~~ particulate matter and sulfate in relation to mortality, ~~and~~after controlling~~ed~~ for potential confounding factors such as smoking status, sex, age, and other factors (Dockery et al. 1993)~~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)~~(Krewski 2000)~~{Dockery, 1993 #103}~~. An extension of the Harvard Six Cities Cohort confirmed the association of mortality with PM2.5 levels, and reported that improvements in PM2.5 levels over the study time period were associated with decreased mortality risk (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 found a linear relationship of PM2.5 levels and mortality from all causes, cardiovascular causes, and from lung cancer ~~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. For example, the authors used county-level COPD risk as an estimate of smoking prevalence, because individual-level measures of smoking were not available. 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 percent% increased risk of cardiovascular disease and a 76 percent% increased risk of death from cardiovascular causes for each additional 10 µg/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. The WHI study results accounted for the potential confounding effects of several factors, including medical risk factors for cardiovascular disease, measures of socioeconomic status, and cigarette smoking. 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). These results accounted for

several potential confounders, including smoking status and history, medical risk factors for cardiovascular disease, and area-level measures of socioeconomic status. This study did not evaluate PM2.5 exposures.

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 μg/m^3 increase in PM2.5 was associated with approximately a 7 percent% increase in mortality from natural causes.

Examples of studies eEstimatesing of mortality risks associated with and long-term PM2.5 levels from recent studies are shown in the figure below. The recent evidence is consistent with past studies, showing increased risk of premature death with increased PM2.5 exposures. For cause-specific mortality, consistent positive associations are seen with cardiovascular mortality endpoints and with lung cancer deaths, but weak associations are seen with overall respiratory mortality.
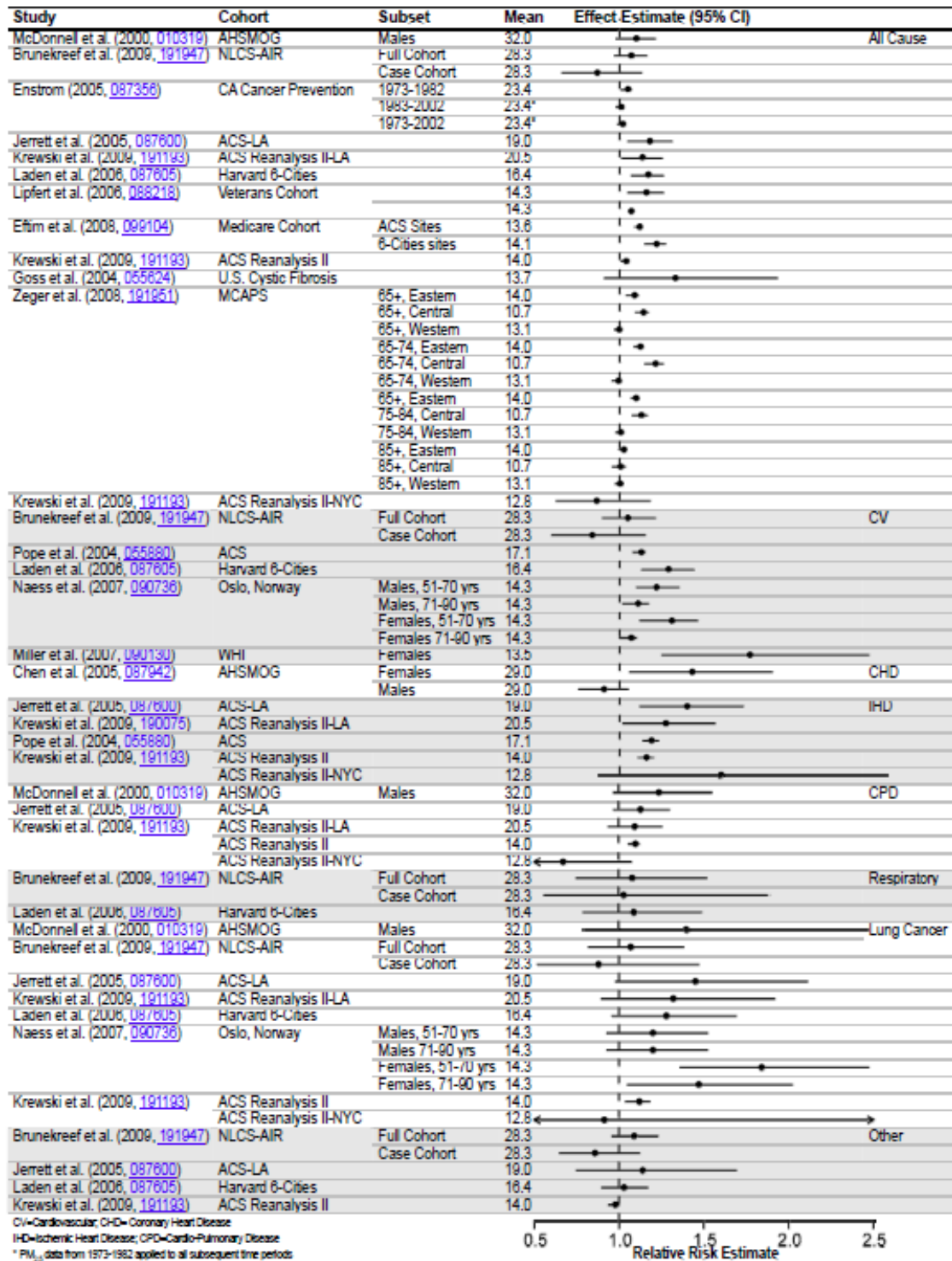
Study	Cohort	Subset	Mean	Effect Estimate (95% CI)	
McDonnell et al. (2000, 010319)	AHSMOG	Males	32.0		All Cause
Brunekreef et al. (2009, 191947)	NLCS-AIR	Full Cohort	28.3		
		Case Cohort	28.3		
Enstrom (2005, 087356)	CA Cancer Prevention	1973-1982	23.4		
		1983-2002	23.4*		
		1973-2002	23.4*		
Jerrett et al. (2005, 087600)	ACS-LA		19.0		
Krewski et al. (2009, 191193)	ACS Reanalysis II-LA		20.5		
Laden et al. (2006, 087605)	Harvard 6-Cities		16.4		
Lipfert et al. (2006, 088218)	Veterans Cohort		14.3		
			14.3		
Eftim et al. (2008, 099104)	Medicare Cohort	ACS Sites	13.6		
		6-Cities sites	14.1		
Krewski et al. (2009, 191193)	ACS Reanalysis II		14.0		
Goss et al. (2004, 055624)	U.S. Cystic Fibrosis		13.7		
Zeger et al. (2008, 191951)	MCAPS	65+, Eastern	14.0		
		65+, Central	10.7		
		65+, Western	13.1		
		65-74, Eastern	14.0		
		65-74, Central	10.7		
		65-74, Western	13.1		
		65+, Eastern	14.0		
		75-84, Central	10.7		
		75-84, Western	13.1		
		85+, Eastern	14.0		
		85+, Central	10.7		
		85+, Western	13.1		
Krewski et al. (2009, 191193)	ACS Reanalysis II-NYC		12.8		
Brunekreef et al. (2009, 191947)	NLCS-AIR	Full Cohort	28.3		CV
		Case Cohort	28.3		
Pope et al. (2004, 055880)	ACS		17.1		
Laden et al. (2006, 087605)	Harvard 6-Cities		16.4		
Naess et al. (2007, 090736)	Oslo, Norway	Males, 51-70 yrs	14.3		
		Males, 71-90 yrs	14.3		
		Females, 51-70 yrs	14.3		
		Females 71-90 yrs	14.3		
Miller et al. (2007, 090130)	WHI	Females	13.5		
Chen et al. (2005, 087942)	AHSMOG	Females	29.0		CHD
		Males	29.0		
Jerrett et al. (2005, 087600)	ACS-LA		19.0		IHD
Krewski et al. (2009, 190075)	ACS Reanalysis II-LA		20.5		
Pope et al. (2004, 055880)	ACS		17.1		
Krewski et al. (2009, 191193)	ACS Reanalysis II		14.0		
	ACS Reanalysis II-NYC		12.8		
McDonnell et al. (2000, 010319)	AHSMOG	Males	32.0		CPD
Jerrett et al. (2005, 087600)	ACS-LA		19.0		
Krewski et al. (2009, 191193)	ACS Reanalysis II-LA		20.5		
	ACS Reanalysis II		14.0		
	ACS Reanalysis II-NYC		12.8		
Brunekreef et al. (2009, 191947)	NLCS-AIR	Full Cohort	28.3		Respiratory
		Case Cohort	28.3		
Laden et al. (2006, 087605)	Harvard 6-Cities		16.4		
McDonnell et al. (2000, 010319)	AHSMOG	Males	32.0		Lung Cancer
Brunekreef et al. (2009, 191947)	NLCS-AIR	Full Cohort	28.3		
		Case Cohort	28.3		
Jerrett et al. (2005, 087600)	ACS-LA		19.0		
Krewski et al. (2009, 191193)	ACS Reanalysis II-LA		20.5		
Laden et al. (2006, 087605)	Harvard 6-Cities		16.4		
Naess et al. (2007, 090736)	Oslo, Norway	Males, 51-70 yrs	14.3		
		Males 71-90 yrs	14.3		
		Females, 51-70 yrs	14.3		
		Females, 71-90 yrs	14.3		
Krewski et al. (2009, 191193)	ACS Reanalysis II		14.0		
	ACS Reanalysis II-NYC		12.8		
Brunekreef et al. (2009, 191947)	NLCS-AIR	Full Cohort	28.3		Other
		Case Cohort	28.3		
Jerrett et al. (2005, 087600)	ACS-LA		19.0		
Laden et al. (2006, 087605)	Harvard 6-Cities		16.4		
Krewski et al. (2009, 191193)	ACS Reanalysis II		14.0		

CV=Cardiovascular; CHD=Coronary Heart Disease;
IHD=Ischemic Heart Disease; CPD=Cardio-Pulmonary Disease
* PM₂.₅ data from 1973-1982 applied to all subsequent time periods

Relative Risk Estimate: 0.5 1.0 1.5 2.0 2.5

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. CV=cardiovascular, CHD=coronary heart disease, IHD=ischemic heart disease, CPD=cardiopulmonary disease.

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. Over 40 potential confounders were included in the statistical models, and included individual-level variables (e.g. smoking, diet, demographic, and other factors) and neighborhood-level variables (e.g. unemployment, poverty, income inequality, racial composition). The authors noted that mortality rates differ in urban areas compared to non-urban areas, and adjusted for urban/rural status in the ~~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 μg/m^3 increase in PM2.5 was associated with a 20 percent~~%~~ risk increase in mortality from ischemic heart disease, but no associations were found with all-cause, cardiovascular, or lung cancer mortality. A 10 μg/m^3 increase in PM10 was associated with increased risk of ischemic heart disease and incident stroke. These results accounted for several individual- and neighborhood-level factors, including smoking, second-hand smoke, medical risk factors for cardiovascular disease, and indicators of socioeconomic status.

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). Both studies adjusted for several individual- and neighborhood-level covariates, including smoking status and indicators of socioeconomic status.
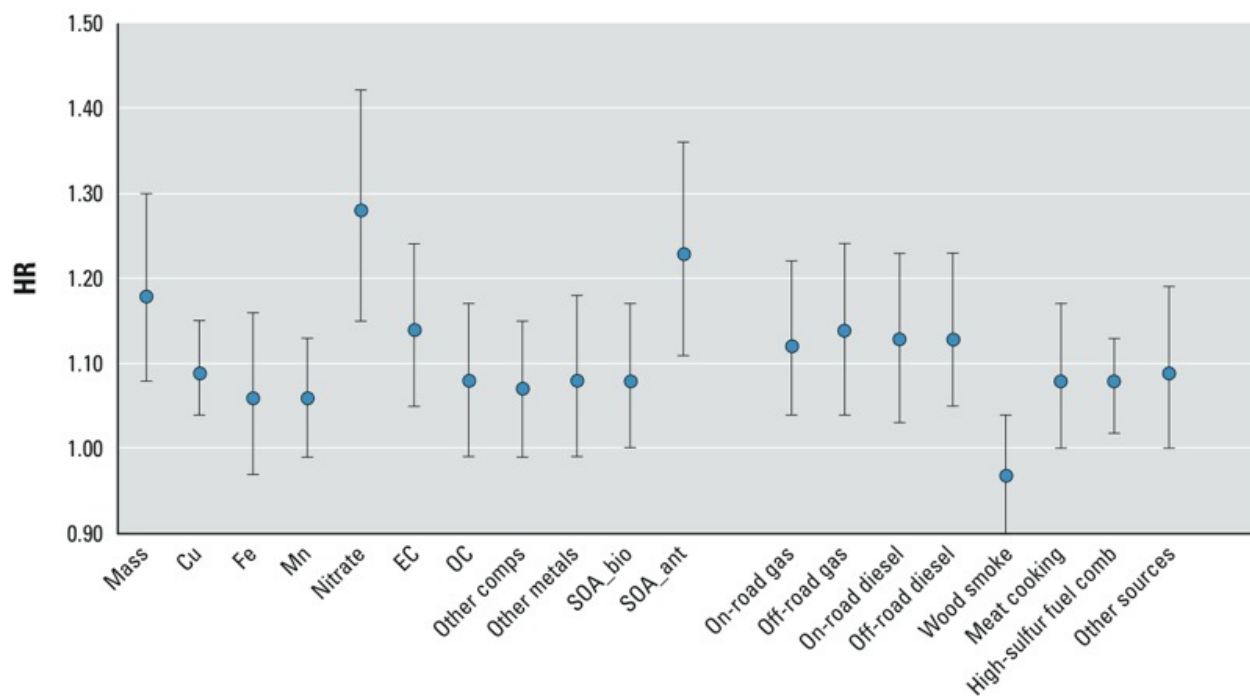

FIGURE I-7

Association of PM2.5 constituents and sources with Ischemic Heart Disease mortality (Hazard Ratios and 95 percent% 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 study adjusted for several potential confounding factors, including demographic factors, smoking, body mass index, and other factors.

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 percent% increase in cardiovascular disease mortality risk for each additional 10 μg/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. This study adjusted for several potential confounders, including demographic factors, smoking, and indicators of socioeconomic status.

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-98, HR refers to the "hazard ratio" expressed for a 10 μg/m^3 change in PM2.5 exposure, followed by the 95 percent% 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/m³ 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)

*These covariates included several measures of smoking.
(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.

At the time of the 2009 ISA, few studies had examined long-term exposures to chemical-specific PM constituents or compared source-specific PM effects on mortality (U.S. EPA 2009). The 2009 ISA discussed only two studies that used direct measurements of PM constituents other than sulfates: the Veteran's Cohort (Lipfert et al. 2006) and the Netherlands Cohort Study (Beelen et al. 2008){Ozkaynak, 1987 #387}. These studies found mortality associations with long-term exposures to traffic pollutants, nitrates and sulfates.

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).

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. The study accounted for the potential influence of sociodemographic factors, lipid status, smoking, diabetes, body mass index, and geographical location. 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, and accounted for the several potential confounding factors, such as sociodemographic factors, medical risk factors for cardiovascular disease, and cigarette smoking (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, and the results accounted for potential confounding by smoking status and history, medical risk factors for cardiovascular disease, and area-level measures of socioeconomic status. 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, poorly controlled asthma, and decreased lung function in children (U.S. EPA 2009; Guarnieri et al. 2014). Since many of the studies of children included survey measures, these studies typically controlled for the potential confounding effect of tobacco smoking by the child and exposure to second-hand smoke at home, and some studies were also able to account for exposure to maternal smoking *in utero*.

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, while those who moved to areas with higher PM10 and NO_2 showed declines in lung function growth rates (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~~ four 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 long-term average ~~high~~ PM2.5 levels ≥13.7 µg/m^3 ~~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 µg/m^3 increase in PM2.5 was associated with a 20 percent~~%~~ increased risk of incident asthma and a 14 percent~~%~~ 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 Emerging Areas of Interest

Beyond cardiovascular, respiratory and mortality effects, the U.S. EPA 2009 ISA review concluded that the evidence ~~assessed~~available at the time was suggestive of a causal relationship between long-term exposures to PM and reproductive/developmental effects, as well as cancer. Since the 2009 ISA, there have been ~~some important~~several studies conducted that evaluated these health endpoints in relation to PM exposures, as well as studies of metabolic syndrome and neurological health outcomes. Because of the relatively long time gap since the latest ISA for PM, and because the SCAB exceeds the federal standards ~~is currently not in attainment~~ for PM2.5, these health endpoints are discussed briefly here, with a focus on studies conducted since the 2009 ISA, and studies conducted in California or in the SCAB.

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~~More recently, 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. Additionally, the study analyzed whether the association between PM2.5 and lung cancer differed by smoking status, and found positive associations for each smoking status group (current smokers, former smokers, and never-smokers).

A recent study from the Adventist Health and Smog Study-2 (AHSMOG-2) cohort in the U.S. and Canada reported that a 10 ug/m^3 increase in ambient PM2.5 increased the risk of lung cancer incidence by about 40 percent~~%~~, after accounting for ozone exposures (Gharibvand et al. 2016). Because all participants are non-smokers, with over 80 percent~~%~~ never having smoked, and with the former smokers having an average of 24 years between quitting smoking and ~~havingreceiving a~~being

diagnosed with lung cancer diagnosis, the likelihood of confounding by smoking in this cohort is much lower than in most other populations. Another recent study conducted in California evaluated air pollution in relation to survival after being diagnosed with lung cancer, and found that patients living in areas with higher NO_2, PM2.5 and PM10 had shorter survival times, particularly for those patients who were diagnosed at earlier stages of lung cancer (Eckel et al. 2016). Few other studies have evaluated air pollution effects on lung cancer survival, so this study represents a relatively newer area of research.

Long-Term Particulate Matter Exposures and Reproductive Health Outcomes

The U.S. EPA 2009 ISA review concluded that existing evidence is suggestive of a link between PM2.5 and reproductive health effects.

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 the 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 μg/m³ increase in PM2.5 exposures during pregnancy was linked to a 2.5 percent% 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). 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). Among these studies, Oone 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).

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 of 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 percent~~%~~ 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.

<u>Neurological Health Outcomes</u>

A 2012 review conducted by a panel of research scientists convened by the National Institute of Environmental Health Sciences identified several studies that reported links between outdoor air pollution and central nervous system effects, such as decreased cognitive function, Alzheimer's disease, Parkinson's disease, and impacts on behavioral testing and development in childhood (Block et al. 2012). Toxicological studies ~~This review paper also described toxicological studies that provide information regarding potential biological mechanisms~~suggest that the damage may be caused through an oxidative stress pathway, and demonstrate that ~~discussed some components of air pollution that may be responsible for these adverse effects, noting the ability of~~ PM can ~~to~~ be inhaled into the lungs and translocated to the brain, and ~~for~~that ultrafine particles to reach the brain through the olfactory nerve (Peters et al. 2006). Some more recent studies have evaluated neurological impacts of ~~PM2.5~~PM, ranging from studies of ~~including neurodegenerative diseases cognitive function in~~ older adults to prenatal exposures~~and developmental disorders (including autism spectrum disorder) in children~~. The Normative Aging Study evaluated older men in Boston, MA, and reported an association between black carbon (a marker of traffic exhaust) and cognitive function, as measured through cognitive tests (Power et al. 2011). ~~{Block, 2012 #407}~~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). A study of school children in Spain reported that children attending schools with higher levels of air pollution, as measured by elemental carbon (a marker of diesel exhaust), NO$_2$, and ultrafine particles, experienced smaller growth in several cognitive measures (Sunyer et al. 2015).

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 percent% increased odds of autism with a 4.68 μg/m³ increase in PM2.5; the effect estimate increased to 15 percent% when accounting for ozone in the statistical models (Becerra et al. 2013). A California-based study found that an 8.7 μg/m³ 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.

Long-Term Particulate Matter Exposures and Newer Health EndpointsMetabolic Syndrome

Metabolic syndromes, which is the clustering of several known risk factors for cardiovascular disease (Huang 2009), are is a 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 markers of 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). Several Some recent studies published since the 2009 ISA have investigated particulate matter exposures in relation to metabolic syndrome. AMore recently, a Swiss epidemiological study reported that long-term PM10 exposures were associated with increased risk of metabolic syndrome (Eze et al. 2015). Two other human studies found that people with metabolic syndrome exposed to particulate matter air pollution experienced cardiovascular effects and worsening insulin resistance (Devlin et al. 2014; Brook et al. 2016). Some recent animal studies have also reported impacts of PM on the development of obesity and metabolic syndrome, and that animals with pre-existing metabolic syndrome may be more sensitive to the cardiovascular effects of PM exposure (Brocato et al. 2014; Wagner et al. 2014; Wei et al. 2016).

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, PM2.5, or PM10-2.5 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 causal determinations are depicted in Table I-9.

TABLE I-9

Summary of U.S. EPA's 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)

In A 2013, a 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). However, a more recent assessment of the studies published since that time suggest that UFP's may be more harmful compared to health compared to PM10 and PM2.5 (Li et al. 2016).

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.

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). Ultrafine particles can also enter the brain tissues through the olfactory nerve (Peters et al. 2006). 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. Combined with the slower clearance of UFP's from the alveolar region of the lung, these small particles can delivery a greater amount of toxics to this part of the lung, causing increased inflammation (Li et al. 2016).

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. More specifically, ambient UFP's with a higher polycyclic aromatic hydrocarbon (PAH) content and higher oxidant potential triggered greater allergic inflammation in mice compared to a mixture of fine and ultrafine particles (Li et al. 2009). A related study identified specific proteins that are up-regulated among the exposed mice, which were proteins involved in allergic airway inflammation and immune system response (Kang et al. 2010). These results suggest that UFP's may play a role in the development or exacerbation of asthma, and point to an oxidative stress pathway. , and a related study identified specific proteins that may be the targets {Li, 2016 #392}. Additionally, some experiments using engineered nanoparticles found that the particle exposure led to a suppressed immune response to infections (Li et al. 2016).

Controlled exposures of human volunteers to 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 at 300 µg/m^3 attenuated both acetylcholine and sodium-nitroprusside-induced vasorelaxation (Mills et al. 2011). These exposures were higher than typical ambient concentrations, although the authors state that such concentrations can be found regularly in heavy traffic, occupational settings, and in some of the most polluted cities in the world. 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. Several other human exposures studies have reported effects of UFP's on inflammatory markers, lung function, microvascular function, heart rate and heart rate variability, including effects on people with asthma, diabetes, or metabolic syndrome (Li et al. 2016).

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).~~{Li, 2016 #392}

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). Other epidemiological studies have reported links between UFP exposures both indoors and outdoors with decreased microvascular function and increased systemic ~~{Evans, 2014 #416}~~inflammation in adults (Karottki et al. 2014; Olsen et al. 2014), and with oxidative DNA damage in children (Song et al. 2013).

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). A recent study conducted in Rochester, NY reported that ambient UFP exposures in the prior week were associated with increased risk of asthma-related medical visits ~~to a doctor's office or emergency department where prednisone (an asthma medication) was prescribed~~indicative of asthma exacerbation; the study did not find associations with accumulation mode PM, PM2.5, black carbon, or sulfur dioxide (Evans et al. 2014). 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.

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 (for respiratory effects) and older adults (for cardiovascular effects), 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. Table I-10~~1~~ summarizes the U.S. EPA's 2009 ISA assessment of susceptibility factors for particulate matter.

TABLE I-10

Summary of Evidence for Potential Increased Susceptibility to PM-Related Health Effects

Assessment of Evidence	Potential At Risk Factor
Increased susceptibility to PM	Older Adults (≥65 years) Children (<18 years) Genetic factors Cardiovascular diseases Respiratory illnesses Socioeconomic status (SES) Educational attainment (surrogate of SES) Residential location (surrogate of SES)
Increased susceptibility to PM, but limited studies available	Pregnancy and developmental effects Diabetes Obesity Health status, e.g. nutrition (surrogate of SES)
Did not increase susceptibility to PM	Gender Race/ethnicity
Did not increase susceptibility to PM, but limited studies available	Respiratory contributions to cardiovascular effects

Adapted From (U.S. EPA 2009) Table 8-2

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~~ epidemiologic, controlled human exposure and toxicological studies ~~suggests~~ support the causal determinations for ~~that ambient~~ particulate matter and several categories of health endpoints, with the strongest evidence supporting a causal relationship for PM2.5 exposures with cardiovascular effects and mortality~~, alone or in combination with other coexisting pollutants, is associated with increases in mortality and morbidity in a community~~. Specific cardiovascular effects include cardiovascular deaths, hospital admissions for ischemic heart disease and congestive heart failure, changes in heart rate variability and markers of oxidative stress, and markers of atherosclerosis. ~~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. The scientific evidence also supported a likely causal relationship for PM2.5 exposure with respiratory effects, such as hospital admissions for COPD or respiratory infections, asthma development, asthma or allergy exacerbation, lung cancer, impacts on lung function, lung inflammation, oxidative stress, and airway hyperresponsiveness. Both short-term and long-term particulate matter exposures are linked to health effects in humans. Young children, older adults, and people with pre-existing respiratory or cardiovascular health conditions are among those who may be more susceptible to the adverse effects of PM.

Estimates of the Health Burden of Particulate Matter in the South Coast Air Basin

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, and estimated the deaths associated with exposures above 5.8 µg/m^3, which is an estimate of background PM2.5 (California Air Resources Board 2010a). 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 (South Coast Air Quality Management District 2012). Based on that analysis, the projected annual number of 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 from the 2012 AQMP was 668 deaths in year 2014, and 275 deaths in year 2023. (South Coast Air Quality Management District 2012). In addition, estimated numbers of health conditions prevented per year due to the 2012 AQMP were shown for several other health endpoints, including respiratory and cardiovascular outcomes. The estimates of cases averted in year 2014 were 597 cases of acute bronchitis, 29 to 261 non-fatal heart attacks, 18,384 person-days for lower and upper respiratory symptoms, 153 respiratory emergency room visits, 151 hospital admissions, 287,447 person-days of minor restricted activity, 48,805 work loss days, and 26,910 person-days of asthma attacks. Importantly, these estimates of prevented mortality and morbidity should not be compared to the estimates of deaths attributable to PM2.5 conducted

by CARB, because these analyses are intended to answer different questions. The SCAQMD estimates ~~answer~~address the question of "how many cases are averted due to the adoption of the 2012 AQMP?" while the CARB estimates ~~answer~~address the question of "how many deaths are attributable to PM2.5 exposures above 5.8 µg/m3?". Both analyses provide important information regarding the health impacts of PM2.5.

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). These gases can undergo photochemical reactions to form ground-level ozone, and are important contributors to ozone pollution levels in the SCAB. 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

Summary of U.S. EPA's 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

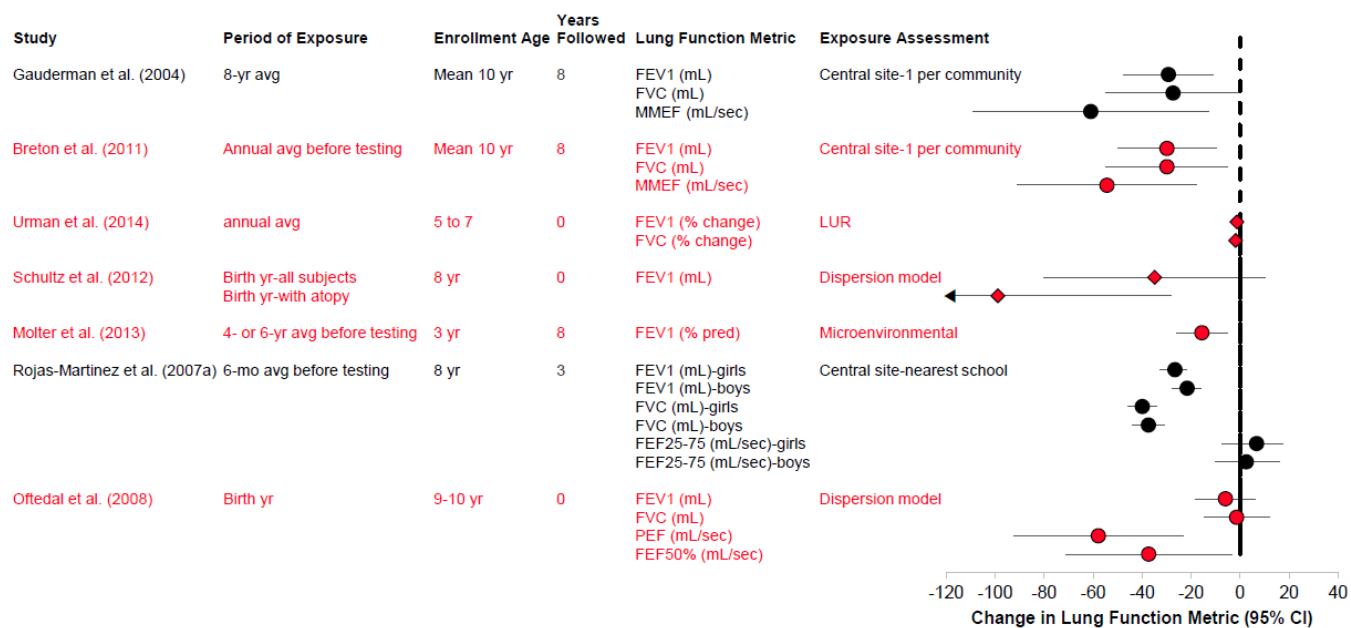(From (U.S. EPA 2016), Table ES-1)

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 NO_2 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-8.
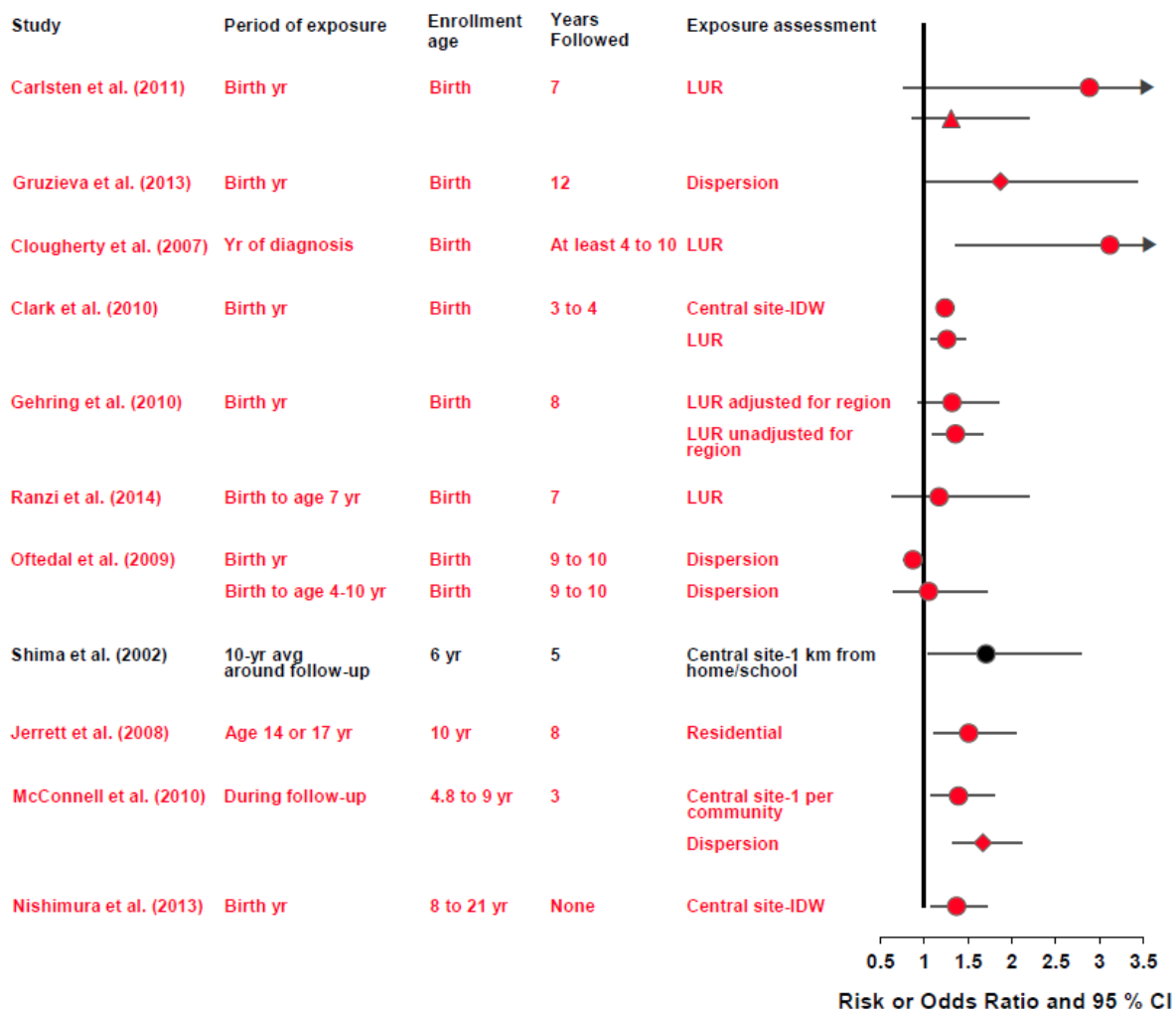
Study	Period of Exposure	Enrollment Age	Years Followed	Lung Function Metric	Exposure Assessment
Gauderman et al. (2004)	8-yr avg	Mean 10 yr	8	FEV1 (mL) FVC (mL) MMEF (mL/sec)	Central site-1 per community
Breton et al. (2011)	Annual avg before testing	Mean 10 yr	8	FEV1 (mL) FVC (mL) MMEF (mL/sec)	Central site-1 per community
Urman et al. (2014)	annual avg	5 to 7	0	FEV1 (% change) FVC (% change)	LUR
Schultz et al. (2012)	Birth yr-all subjects Birth yr-with atopy	8 yr	0	FEV1 (mL)	Dispersion model
Molter et al. (2013)	4- or 6-yr avg before testing	3 yr	8	FEV1 (% pred)	Microenvironmental
Rojas-Martinez et al. (2007a)	6-mo avg before testing	8 yr	3	FEV1 (mL)-girls FEV1 (mL)-boys FVC (mL)-girls FVC (mL)-boys FEF25-75 (mL/sec)-girls FEF25-75 (mL/sec)-boys	Central site-nearest school
Oftedal et al. (2008)	Birth yr	9-10 yr	0	FEV1 (mL) FVC (mL) PEF (mL/sec) FEF50% (mL/sec)	Dispersion model

X-axis: Change in Lung Function Metric (95% CI): -120, -100, -80, -60, -40, -20, 0, 20, 40

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 µg/m$_3$ (Schultz et al., 2012) have not been standardized.

FIGURE I-8

Associations of nitrogen dioxide (NO_2) or the sum of nitric oxide and NO_2 (NO_x) 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-9. The vast majority of these studies found that higher NO_2 exposures were linked to an increased risk or odds of developing asthma among children.

Study	Period of exposure	Enrollment age	Years Followed	Exposure assessment
Carlsten et al. (2011)	Birth yr	Birth	7	LUR
Gruzieva et al. (2013)	Birth yr	Birth	12	Dispersion
Clougherty et al. (2007)	Yr of diagnosis	Birth	At least 4 to 10	LUR
Clark et al. (2010)	Birth yr	Birth	3 to 4	Central site-IDW / LUR
Gehring et al. (2010)	Birth yr	Birth	8	LUR adjusted for region / LUR unadjusted for region
Ranzi et al. (2014)	Birth to age 7 yr	Birth	7	LUR
Oftedal et al. (2009)	Birth yr	Birth	9 to 10	Dispersion
	Birth to age 4-10 yr	Birth	9 to 10	Dispersion
Shima et al. (2002)	10-yr avg around follow-up	6 yr	5	Central site-1 km from home/school
Jerrett et al. (2008)	Age 14 or 17 yr	10 yr	8	Residential
McConnell et al. (2010)	During follow-up	4.8 to 9 yr	3	Central site-1 per community / Dispersion
Nishimura et al. (2013)	Birth yr	8 to 21 yr	None	Central site-IDW

Effect estimates are standardized to a 10-ppb increase in NO₂, 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=NO₂; triangles=NO; diamonds=NOx.

FIGURE I-9

Associations of ambient nitrogen dioxide (NO₂) 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 NO₂ 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 NO₂ levels to estimate exposures (McConnell et al. 2010). Both studies found a positive association between NO₂ exposures and the onset of asthma in these children, however, because NO₂ 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 percent~~%~~ 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 from controlled human exposure studies of ~~when~~ people with chronic obstructive lung disease~~-~~, with some studies reporting no change in symptom score while other studies reporting increased symptom scores when participants were exposed to NO_2 while exercising (U.S. EPA 2016)~~are exposed to low levels of NO2~~.

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 (4000 ppb). 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 also found links with these health outcomes, and the latest assessment by U.S. EPA is that the existing studies are suggestive of a causal relationship for some of these endpoints or inadequate to infer a causal relationship for other endpoints (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, or whether NO$_2$ is simply a marker of near-road air pollution exposure, which includes a mixture of air pollutants, including some air toxics.

Examples of studies reporting an association of mortality with short-term NO$_2$ exposures are shown in the figure below.
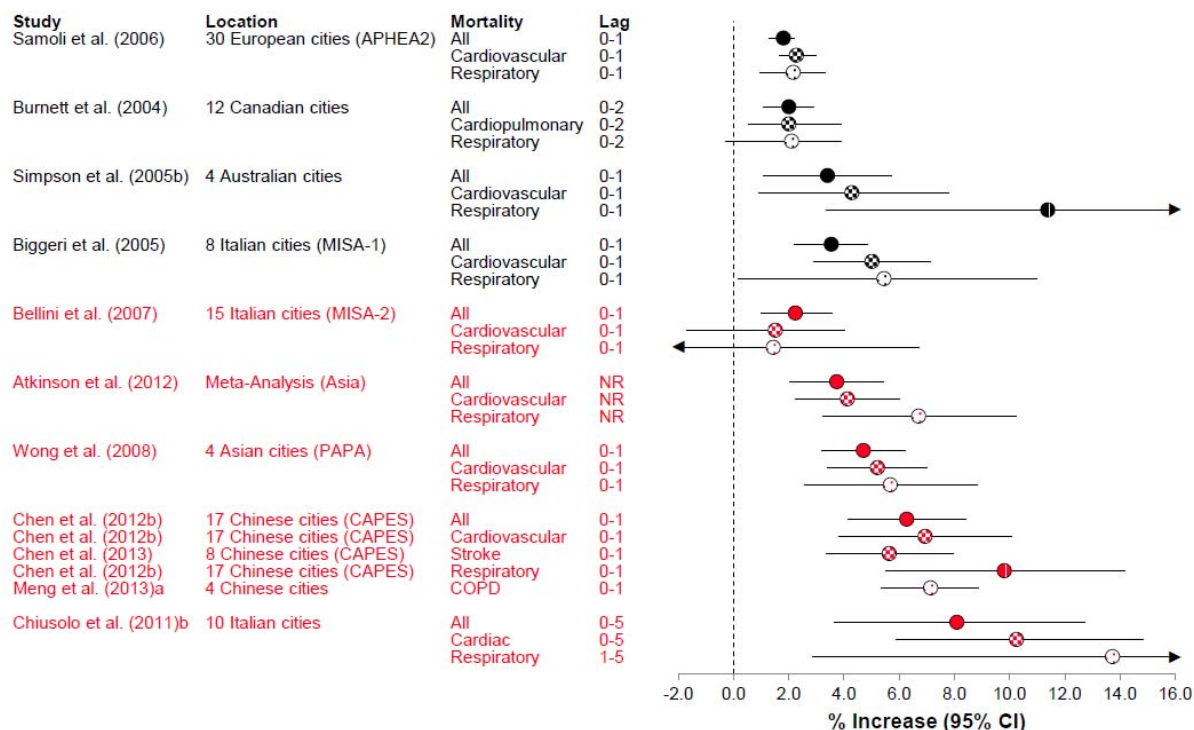
Note: Black symbols = multicity studies evaluated in the 2008 Integrated Science Assessment for Oxides of Nitrogen; Red symbols = recent studies. Filled circle = total mortality; Crosshatch = cardiovascular mortality; Vertical lines = respiratory mortality.

FIGURE I-10

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 (SO$_2$) 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

Summary of U.S. EPA's 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 $\mu g/m^3$ (24-hour average) for sulfates. There is no federal air quality standard for sulfates.

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-13) (U.S. EPA 2010).

TABLE I-13

Summary of U.S. EPA's Causal Determinations 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 percent 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 percent, former smokers: 1.96±1.87 percent, 1-5 cigarettes/day: 2.31±1.94 percent, 6–14 cigarettes/day: 4.39±2.48 percent, 15–24 cigarettes/day: 5.68±2.64 percent, >=25 cigarettes/day: 6.02±2.86 percent) (Hart et al. 2006).

Under controlled laboratory conditions, healthy subjects exposed to CO sufficient to result in 5 percent 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 percent% 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.
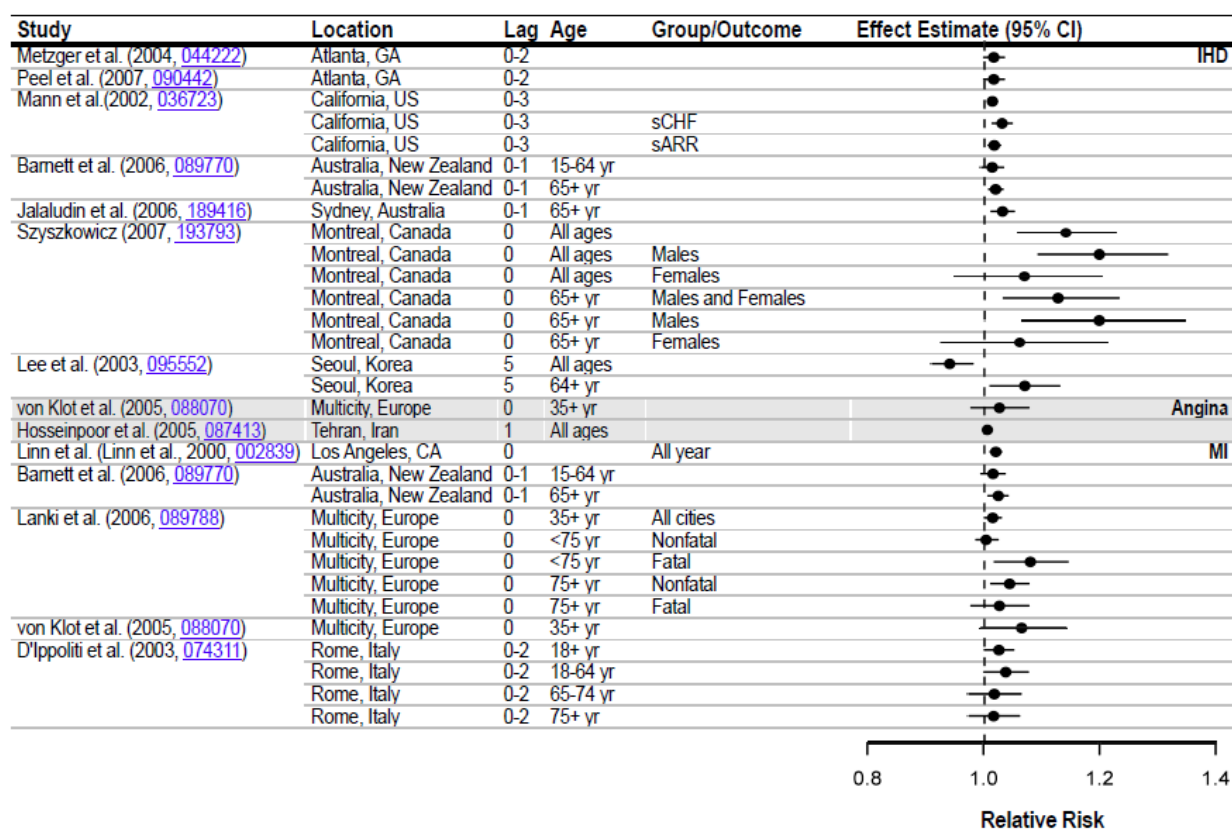
FIGURE I-11

Effect estimates (95 percent% 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 average 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 percent% 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.

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, and there is no lead is recognized as not having a safe lower threshold for health effects (U.S. EPA 2013a)of exposure. 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 SCAB's attainment status for lead is described in the draft 2016 AQMP Chapter 2.

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). Lead can accumulate and be stored in the bone, and this lead in bone can be released into the blood when the bone is metabolized, which happens naturally and continuously. Blood lead is the most common measure of lead exposure, and it represents recent exposure and may be an indicator of total body burden of lead (U.S. EPA 2013a). The following table gives the summary of causality conclusions from the U.S. EPA review, which illustrates the wide range of health effects associated with lead exposure.

TABLE I-14

Summary of U.S. EPA's Causal Determinations for ~~the Relationship Between Exposure to Pb and~~ Health Effects of Lead

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.

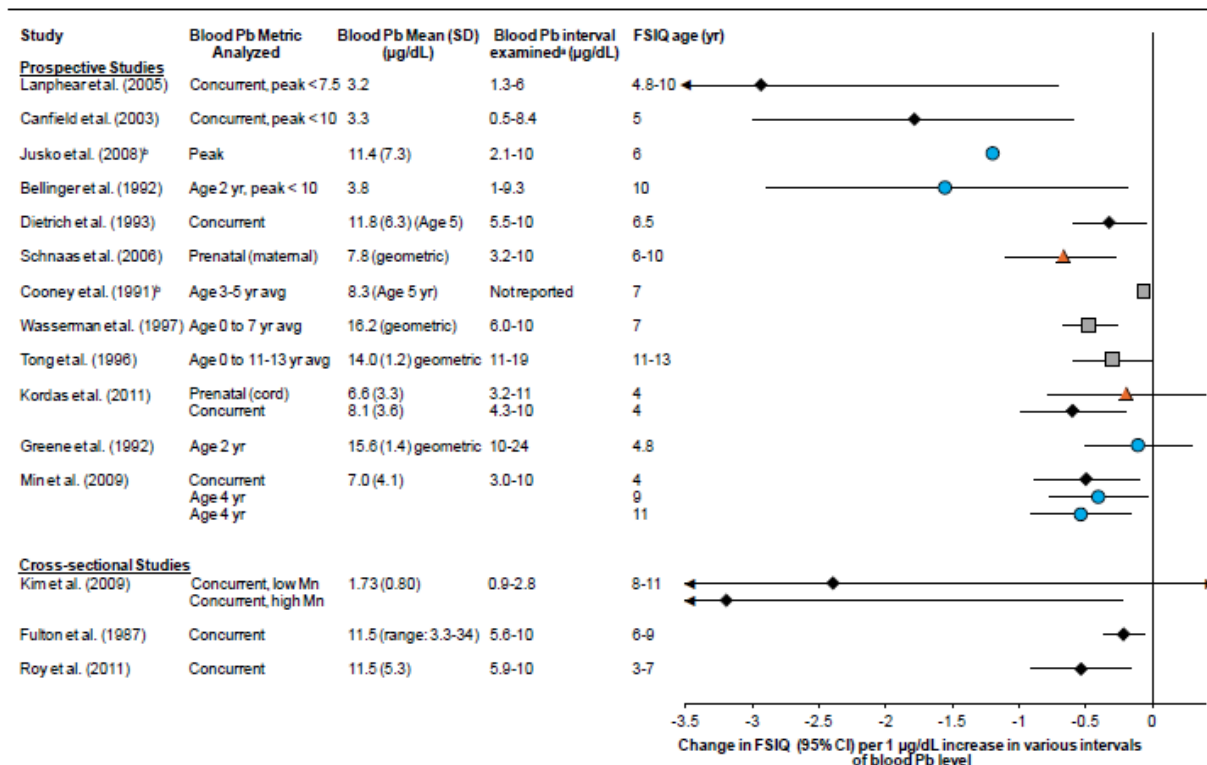| Lowest Observed Effect Blood Lead Level	Neurological Effects	Hematological Effects	Immune Effects
30 µg/dL		Increased urinary δ-aminolevulinic acid	
15 µg/dL	Behavioral disturbances (e.g., inattention, delinquency) Altered electrophysiological responses	Erythrocyte protoporphyrin (EP) elevation	
10 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 ($\uparrow$ serum IgE) and cell-mediated ($\downarrow$ T-cell abundance) immunity
5 µg/dL	$\downarrow$ (???)	$\downarrow$ (???)	
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).

Study	Blood Pb Metric Analyzed	Blood Pb Mean (SD) (μg/dL)	Blood Pb interval examined[a] (μg/dL)	FSIQ age (yr)
Prospective Studies				
Lanphear et al. (2005)	Concurrent, peak <7.5	3.2	1.3-6	4.8-10
Canfield et al. (2003)	Concurrent, peak <10	3.3	0.5-8.4	5
Jusko et al. (2008)[b]	Peak	11.4 (7.3)	2.1-10	6
Bellinger et al. (1992)	Age 2 yr, peak < 10	3.8	1-9.3	10
Dietrich et al. (1993)	Concurrent	11.8 (6.3) (Age 5)	5.5-10	6.5
Schnaas et al. (2006)	Prenatal (maternal)	7.8 (geometric)	3.2-10	6-10
Cooney et al. (1991)[b]	Age 3-5 yr avg	8.3 (Age 5 yr)	Not reported	7
Wasserman et al. (1997)	Age 0 to 7 yr avg	16.2 (geometric)	6.0-10	7
Tong et al. (1996)	Age 0 to 11-13 yr avg	14.0 (1.2) geometric	11-19	11-13
Kordas et al. (2011)	Prenatal (cord)	6.6 (3.3)	3.2-11	4
	Concurrent	8.1 (3.6)	4.3-10	4
Greene et al. (1992)	Age 2 yr	15.6 (1.4) geometric	10-24	4.8
Min et al. (2009)	Concurrent	7.0 (4.1)	3.0-10	4
	Age 4 yr			9
	Age 4 yr			11
Cross-sectional Studies				
Kim et al. (2009)	Concurrent, low Mn	1.73 (0.80)	0.9-2.8	8-11
	Concurrent, high Mn			
Fulton et al. (1987)	Concurrent	11.5 (range: 3.3-34)	5.6-10	6-9
Roy et al. (2011)	Concurrent	11.5 (5.3)	5.9-10	3-7

[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. Chapter 9 of the draft 2016 AQMP describes the Air Toxics Control Plan for the SCAQMD.

Air toxics include many different types of chemicals, and the discussion here will not address all air toxics in a comprehensive manner. However, this section will discuss very briefly diesel particulate matter and volatile organic compounds (VOC's), because diesel particulate matter is the most significant contributor to cancer risk in the South Coast Air Basin, and because some ~~volatile organic compounds~~VOC's are air toxics ~~that also~~are also ~~generate ozone precursors~~, and are ~~therefore~~ part of the control measures proposed in the current ~~and prior~~ Air Quality Management Plan~~s~~.

Diesel Particulate Matter

The California Air Resources Board listed diesel particulate matter as a Toxic Air Contaminant in 19~~9~~8, based on the determination that it was a human carcinogen (California Air Resources Board 2010b)~~9~~. 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 2012b).

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.

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 percent~~%~~ 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 percent% 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. Rresults from the MATES IV study still represent approximately about a -50 percent% reduction in air toxics levels and cancer risk compared to MATES III (conducted in 2004-2006). In addition to the maps in the MATES IV final report (South Coast Air Quality Management District 2015), an interactive map of the MATES IV cancer risks from air toxics calculated using the 2015 OEHHA guidelines is available onthrough this website: http://www.aqmd.gov/home/tools/public.

In 2009, the Advanced Collaborative Emissions Study (ACES) reported that newer diesel engine technologies are very effective in reducing the amount of emissions from diesel trucks, as required by recent regulations (Khalek et al. 2009). In a long-term exposure study published in 2015, rats breathing the lower emissions did not develop cancer, while the rats breathing the higher emissions from older diesel engines (in previous studies) did develop cancer (McDonald et al. 2015). However, the 2015 study did not evaluate whether the PM from the newer engines was any more or less toxic compared to the older engines on a gram per gram basis; the study was not designed to determine such differences. Therefore, without any additional data on the toxicity of PM from the newer diesel engines, the analysis done in the MATES -IV study used the same risk factor for both, applied to the mass of PM. For example, whether a person is exposed to 10 ug/m^3 of particulate matter from a single old diesel engine or several new diesel engines, the cancer risk would be the same because it is calculated based on 10 ug/m^3 of exposure.

In the Particulate Matter section of this Appendix, the vast majority of the studies described evaluated the health effects of total PM2.5 exposures by mass, regardless of whether they were from newer diesel engines, older diesel engines, or other sources. While this new diesel technology is very effective in terms of reducing the amount of emissions from diesel trucks, what people are being exposed to is a total concentration of PM from many sources. Health studies generally use this total concentration to analyze whether or not there is an effect on the specific health outcomes evaluated. In addition, it is important to note that direct PM2.5 emissions from diesel engines represent a small portion of overall PM2.5 exposure. NO$_x$ emissions from diesel engines that eventually lead to PM2.5

formation in the atmosphere, however, represent a larger component of PM2.5 exposure (South Coast Air Quality Management District 2013a; Harley 2014).

Volatile Organic Compounds

VOC's are a class of air pollutants that undergo photochemical reactions in the air to form ozone. It should be noted that there are no state or national ambient air quality standards for VOCs because they are not classified as criteria pollutants. VOCs are regulated, however, because limiting VOC emissions reduces the rate of photochemical reactions that contribute to the formation of ozone.

VOCs are also transformed into organic aerosols in the atmosphere, contributing to higher PM and lower visibility levels. In addition, VOC's that have toxic properties are also regulated as air toxics. Chapter 3 of the draft 2016 AQMP presents data on VOC sources and emissions in the South Coast Air Basin.

Some examples of VOC's that are known to cause health effects include benzene, toluene, ethylbenzene and xylenes (abbreviated BTEX), 1,3-butadiene, formaldehyde, and perchloroethylene. Several of these VOC's are carcinogenic. Based on the MATES IV analysis, benzene, 1,3-butadiene, and carbonyls (formaldehyde and acetaldehyde) together account for approximately 21 percent% of the total cancer risk from air toxics in the SCAB. Not all carcinogenic VOC's are known to cause the same types of cancers, although several are associated with blood cancers. For example, the cancerss most closely associated with long-term benzene exposure are leukemias. Formaldehyde is linked to nasopharyngeal cancer and leukemias, while .1,3-butadiene causes cancers in both the blood and lymphatic systems (International Agency for Research on Cancer 2012a).

Many VOC's can also cause non-cancer health effects. For non-cancer healththese types of health outcomeseffects, 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).

In the MATES IV assessment of chronic non-cancer health risks, the monitored air toxics levels were found to be below the chronic RELs. In other words, the general levels of air toxics in the SCAB are not expected to cause adverse non-cancer health effects. Importantly, the MATES IV monitoring network was designed to characterize the air toxics exposures in the basin overall. Given that ambient monitoring is necessarily conducted at a limited number of locations, and modeling is limited to a spatial resolution of 2km, there may be higher exposures not captured by the fixed-site monitoring. To address this limitation, particularly in some communities with environmental justice concerns, the MATES IV study also included local-scale studies in 3 communities very close to known industrial sources or large mobile source facilities, with a focus on ultrafine particles and diesel PM

emissions. Details of these study results can be found in the MATES IV final report (South Coast Air Quality Management District 2015).

ODORS

Environmental odors are recognized as having the potential to cause health effects and/or quality of life impacts. The theory of "miasma" dates back to Hippocrates in ancient Greek times, and related bad odors to disease. The health effects of environmental odors can vary widely, and depend on the compound causing the odor, the level of the compound, as well as the sensitivity and physiological responses of the person detecting the odor.

Different levels of odor exposure can cause a range of responses and health effects, and the science of odor as a potential health issue was summarized previously by Schiffman and Williams (Schiffman et al. 2005b). There are two key nerves in the nasal cavity involved in odor effects: the olfactory nerve provides the sense of smell, while the trigeminal nerve provides the sense of irritation. At very low levels, an odor can be detected (i.e. odor threshold), and at slightly higher levels, an odor can be recognized and identified. At levels higher than detection or recognition levels, an odor can cause annoyance or intolerance, and at even higher levels, an odor can cause irritation or possible toxicity, if the odor is caused by a compound that is also an air toxic (Schiffman et al. 2005b).

Schiffman and Williams proposed three mechanisms of action for odor symptoms (Schiffman et al. 2005b). In the first mechanism, an odor substance can be at the level that can produce irritation, which triggers the trigeminal nerve. This mechanism is considered a toxic effect because symptoms appear when the chemical concentration is at or above the irritation level; here, the odor serves only as the marker of the toxic effect. In the second mechanism, the odor compound is below the irritation level but above odor detection thresholds, which can result in odor annoyance. This mechanism is relatively common among environmental odors, and has been studied in communities exposed to odors from landfills, hazardous waste sites or concentrated animal feeding operations (CAFO's) (Shusterman et al. 1991; Schiffman et al. 2005a; Heaney et al. 2011; Schinasi et al. 2011; Blanes-Vidal et al. 2012; Hooiveld et al. 2015). In this mechanism, the health effect is not a toxicological effect, and the dose does not necessarily correlate well with the effect in these instances. Genetic factors, previous exposure ("learning"), and beliefs about the safety of the odor may play important roles in these odors causing health symptoms (Shusterman 2001). The third proposed mechanism is when an odor substance is present along with a co-pollutant or endotoxin that is capable of producing health effects. In this mechanism, the effect is also a toxic effect, but the odor serves as a marker of the presence of a mixture that includes a toxic compound; if the co-pollutant were not present, no health effect would be expected in this scenario.

Individual characteristics can play important roles in altering an individual's response to an odor. Factors that can influence odor perception include age, genetics, gender, medical history (including mental health, neurological conditions, and other health conditions), health-related behaviors (tobacco, alcohol), and occupational and environmental factors (Greenberg et al. 2013; Wilson et al. 2014; Agency for Toxic Substances and Disease Registry 2016). Additionally, an individual's cognitive

associations with the odor prior to an exposure can result in increased reporting of health-related symptoms after exposure (Shusterman et al. 1991; Shusterman 2001; Greenberg et al. 2013). Common symptoms associated with environmental odor exposures include headache, nasal congestion, eye, nose and throat irritation, hoarseness or sore throat, cough, chest tightness, shortness of breath, wheezing heart palpitations, nausea, drowsiness, and mental depression (Agency for Toxic Substances and Disease Registry 2016). If the concentrations of the odor compound are below irritation levels, then the symptoms are not expected to persist once the person is no longer exposed; however, being exposed to odor levels at or above irritation levels for longer periods of time may cause symptoms that persist after moving out of the exposure area (Agency for Toxic Substances and Disease Registry 2016).

CONCLUSIONS

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. Importantly, the health effects of air pollution extend beyond respiratory effects, and there is substantial evidence that air pollution (including particulate matter and ozone) exposures cause cardiovascular morbidity and mortality. Some air pollutants, such as diesel PM, lead, and several other air toxics, have been linked to increased cancer risk. Health studies have also identified populations who may be more susceptible to the adverse effects of air pollution, such as children, older adults, low SES communities, people with certain pre-existing health conditions, and people with certain genetic factors. Understanding the impacts of air pollution on these more susceptible populations can help inform policies that better protect public health, for example, in setting standards for criteria air pollutants, and in the development of methods to evaluate air toxics health risks. Continued research on the effects of specific PM constituents and ultrafine particles will be important in furthering the understanding of how these pollutants affect human health.

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 (NAAQS) which, in the judgment of the Administrator of the U.S. EPA, are necessary to protect public health. Chapter 8 of the draft 2016 AQMP provides an overview of the extensive, multi-year, public process involved in setting federal air quality standards. Assessments of the scientific evidence from health studies is an important part of the process, and has helped inform revisions to the federal air pollution standards. 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, with regard to key developments in the understanding of the health effects of these pollutants.
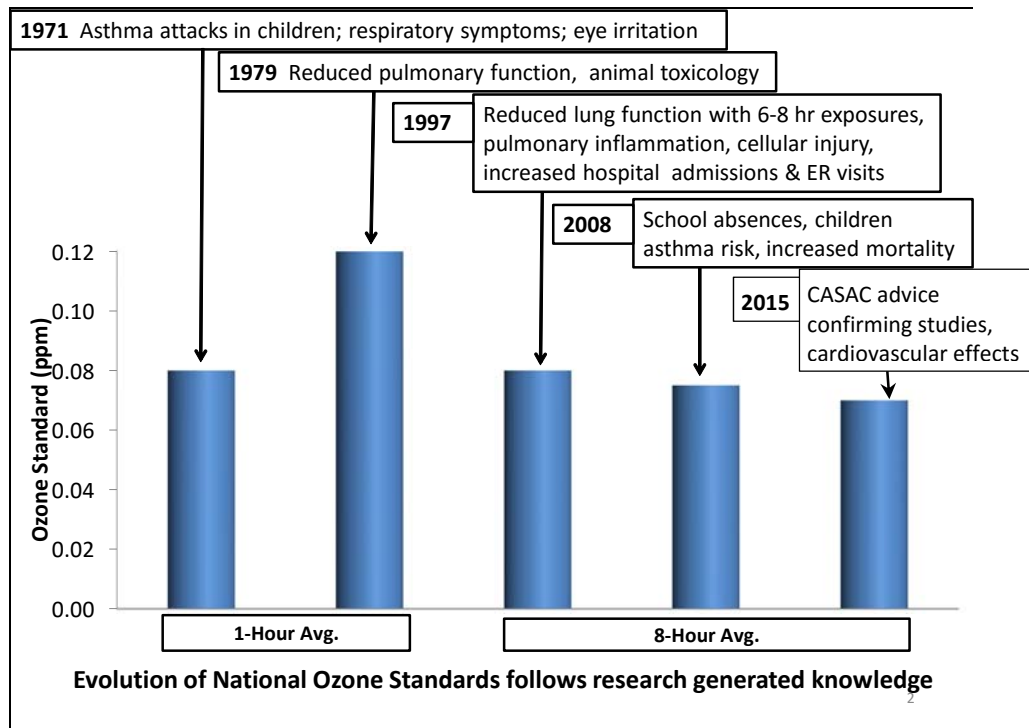
FIGURE I-15

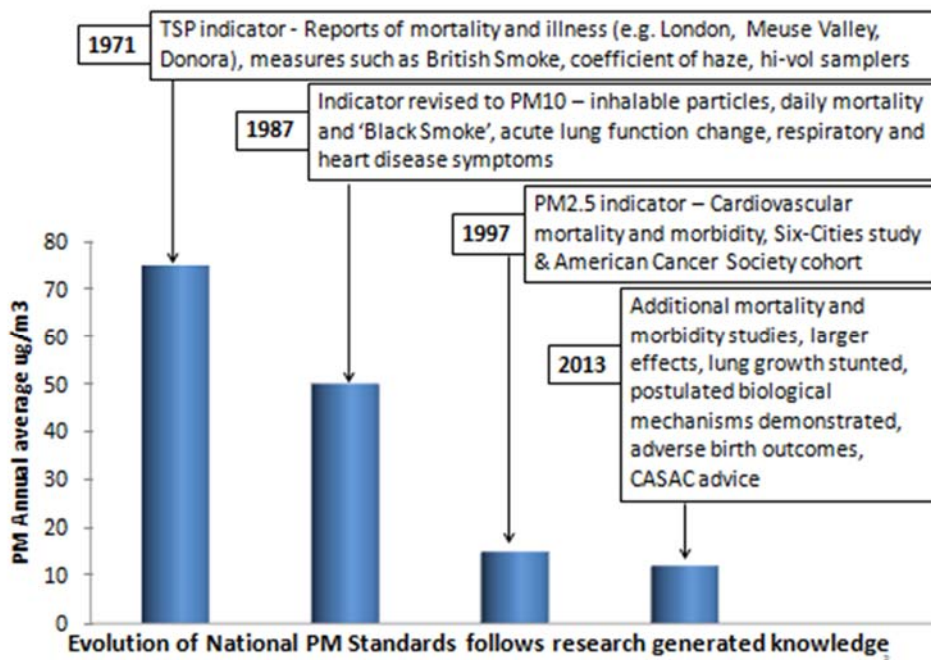Historical Context to Revisions of NAAQS for Ozone

FIGURE I- 16

Historical Context to Revisions of NAAQS for PM

REFERENCES

Abbey, D. E., N. Nishino, W. F. McDonnell, R. J. Burchette, S. F. Knutsen, W. Lawrence Beeson and J. X. Yang (1999). "Long-term inhalable particles and other air pollutants related to mortality in nonsmokers." Am J Respir Crit Care Med **159**(2): 373-382.

Agency for Toxic Substances and Disease Registry. (2016, February 29, 2016). "Frequently Asked Questions (FAQ)." Retrieved November 18, 2016, from https://www.atsdr.cdc.gov/odors/faqs.html.

Akinbami, L. J., C. D. Lynch, J. D. Parker and T. J. Woodruff (2010). "The association between childhood asthma prevalence and monitored air pollutants in metropolitan areas, United States, 2001-2004." Environ Res **110**(3): 294-301.

Alexis, N. E. and C. Carlsten (2014). "Interplay of air pollution and asthma immunopathogenesis: a focused review of diesel exhaust and ozone." Int Immunopharmacol **23**(1): 347-355.

American Thoracic Society (1996a). "Health effects of outdoor air pollution. Committee of the Environmental and Occupational Health Assembly of the American Thoracic Society." Am J Respir Crit Care Med **153**(1): 3-50.

American Thoracic Society (1996b). "Health effects of outdoor air pollution. Part 2. Committee of the Environmental and Occupational Health Assembly of the American Thoracic Society." Am J Respir Crit Care Med **153**(2): 477-498.

Ancona, C., C. Badaloni, F. Mataloni, A. Bolignano, S. Bucci, G. Cesaroni, R. Sozzi, M. Davoli and F. Forastiere (2015). "Mortality and morbidity in a population exposed to multiple sources of air pollution: A retrospective cohort study using air dispersion models." Environmental Research **137**: 467-474.

Araujo, J. A., B. Barajas, M. Kleinman, X. Wang, B. J. Bennett, K. W. Gong, M. Navab, J. Harkema, C. Sioutas, A. J. Lusis and A. E. Nel (2008). "Ambient particulate pollutants in the ultrafine range promote early atherosclerosis and systemic oxidative stress." Circ Res **102**(5): 589-596.

Atkinson, R. W., A. Analitis, E. Samoli, G. W. Fuller, D. C. Green, I. S. Mudway, H. R. Anderson and F. J. Kelly (2016). "Short-term exposure to traffic-related air pollution and daily mortality in London, UK." J Expo Sci Environ Epidemiol **26**(2): 125-132.

Avol, E. L., W. J. Gauderman, S. M. Tan, S. J. London and J. M. Peters (2001). "Respiratory effects of relocating to areas of differing air pollution levels." Am J Respir Crit Care Med **164**(11): 2067-2072.

Bartell, S. M., J. Longhurst, T. Tjoa, C. Sioutas and R. J. Delfino (2013). "Particulate air pollution, ambulatory heart rate variability, and cardiac arrhythmia in retirement community residents with coronary artery disease." Environmental Health Perspectives **121**(10): 1135-1141.

Basagana, X., B. Jacquemin, A. Karanasiou, B. Ostro, X. Querol, D. Agis, E. Alessandrini, J. Alguacil, B. Artinano, M. Catrambone, J. D. de la Rosa, J. Diaz, A. Faustini, S. Ferrari, F. Forastiere, K. Katsouyanni, C. Linares, C. Perrino, A. Ranzi, I. Ricciardelli, E. Samoli, S. Zauli-Sajani, J. Sunyer and M. Stafoggia (2015). "Short-term

effects of particulate matter constituents on daily hospitalizations and mortality in five South-European cities: results from the MED-PARTICLES project." Environ Int **75**: 151-158.

Basu, R., M. Harris, L. Sie, B. Malig, R. Broadwin and R. Green (2014). "Effects of fine particulate matter and its constituents on low birth weight among full-term infants in California." Environ Res **128**: 42-51.

Basu, R. and J. M. Samet (2002). "Relation between elevated ambient temperature and mortality: a review of the epidemiologic evidence." Epidemiol Rev **24**(2): 190-202.

Basu, R., T. J. Woodruff, J. D. Parker, L. Saulnier and K. C. Schoendorf (2004). "Comparing exposure metrics in the relationship between PM2.5 and birth weight in California." J Expo Anal Environ Epidemiol **14**(5): 391-396.

Becerra, T. A., M. Wilhelm, J. Olsen, M. Cockburn and B. Ritz (2013). "Ambient air pollution and autism in Los Angeles county, California." Environ Health Perspect **121**(3): 380-386.

Beelen, R., G. Hoek, P. A. van den Brandt, R. A. Goldbohm, P. Fischer, L. J. Schouten, M. Jerrett, E. Hughes, B. Armstrong and B. Brunekreef (2008). "Long-term effects of traffic-related air pollution on mortality in a Dutch cohort (NLCS-AIR study)." Environmental Health Perspectives **116**(2): 196-202.

Beelen, R., O. Raaschou-Nielsen, M. Stafoggia, Z. J. Andersen, G. Weinmayr, B. Hoffmann, K. Wolf, E. Samoli, P. Fischer, M. Nieuwenhuijsen, P. Vineis, W. W. Xun, K. Katsouyanni, K. Dimakopoulou, A. Oudin, B. Forsberg, L. Modig, A. S. Havulinna, T. Lanki, A. Turunen, B. Oftedal, W. Nystad, P. Nafstad, U. De Faire, N. L. Pedersen, C. G. Ostenson, L. Fratiglioni, J. Penell, M. Korek, G. Pershagen, K. T. Eriksen, K. Overvad, T. Ellermann, M. Eeftens, P. H. Peeters, K. Meliefste, M. Wang, B. Bueno-de-Mesquita, D. Sugiri, U. Kramer, J. Heinrich, K. de Hoogh, T. Key, A. Peters, R. Hampel, H. Concin, G. Nagel, A. Ineichen, E. Schaffner, N. Probst-Hensch, N. Kunzli, C. Schindler, T. Schikowski, M. Adam, H. Phuleria, A. Vilier, F. Clavel-Chapelon, C. Declercq, S. Grioni, V. Krogh, M. Y. Tsai, F. Ricceri, C. Sacerdote, C. Galassi, E. Migliore, A. Ranzi, G. Cesaroni, C. Badaloni, F. Forastiere, I. Tamayo, P. Amiano, M. Dorronsoro, M. Katsoulis, A. Trichopoulou, B. Brunekreef and G. Hoek (2014). "Effects of long-term exposure to air pollution on natural-cause mortality: an analysis of 22 European cohorts within the multicentre ESCAPE project." Lancet **383**(9919): 785-795.

Bell, M. L. and F. Dominici (2008). "Effect modification by community characteristics on the short-term effects of ozone exposure and mortality in 98 US communities." Am J Epidemiol **167**(8): 986-997.

Bell, M. L., F. Dominici and J. M. Samet (2005). "A meta-analysis of time-series studies of ozone and mortality with comparison to the national morbidity, mortality, and air pollution study." Epidemiology **16**(4): 436-445.

Bell, M. L., A. McDermott, S. L. Zeger, J. M. Samet and F. Dominici (2004). "Ozone and short-term mortality in 95 US urban communities, 1987-2000." Jama **292**(19): 2372-2378.

Bell, M. L., A. Zanobetti and F. Dominici (2014). "Who is more affected by ozone pollution? A systematic review and meta-analysis." Am J Epidemiol **180**(1): 15-28.

Berhane, K., C. C. Chang, R. McConnell, W. J. Gauderman, E. Avol, E. Rapapport, R. Urman, F. Lurmann and F. Gilliland (2016). "Association of Changes in Air Quality With Bronchitic Symptoms in Children in California, 1993-2012." Jama **315**(14): 1491-1501.

Blanes-Vidal, V., H. Suh, E. S. Nadimi, P. Lofstrom, T. Ellermann, H. V. Andersen and J. Schwartz (2012). "Residential exposure to outdoor air pollution from livestock operations and perceived annoyance among citizens." Environ Int **40**: 44-50.

Block, M. L., A. Elder, R. L. Auten, S. D. Bilbo, H. Chen, J. C. Chen, D. A. Cory-Slechta, D. Costa, D. Diaz-Sanchez, D. C. Dorman, D. R. Gold, K. Gray, H. A. Jeng, J. D. Kaufman, M. T. Kleinman, A. Kirshner, C. Lawler, D. S. Miller, S. S. Nadadur, B. Ritz, E. O. Semmens, L. H. Tonelli, B. Veronesi, R. O. Wright and R. J. Wright (2012). "The outdoor air pollution and brain health workshop." Neurotoxicology **33**(5): 972-984.

Bobak, M. and D. A. Leon (1999). "Pregnancy outcomes and outdoor air pollution: an ecological study in districts of the Czech Republic 1986-8." Occup Environ Med **56**(8): 539-543.

Brauer, M., G. Hoek, H. A. Smit, J. C. de Jongste, J. Gerritsen, D. S. Postma, M. Kerkhof and B. Brunekreef (2007). "Air pollution and development of asthma, allergy and infections in a birth cohort." Eur Respir J **29**(5): 879-888.

Brocato, J., H. Sun, M. Shamy, T. Kluz, M. A. Alghamdi, M. I. Khoder, L. C. Chen and M. Costa (2014). "Particulate matter from Saudi Arabia induces genes involved in inflammation, metabolic syndrome and atherosclerosis." J Toxicol Environ Health A **77**(13): 751-766.

Brook, R. D., B. Franklin, W. Cascio, Y. Hong, G. Howard, M. Lipsett, R. Luepker, M. Mittleman, J. Samet, S. C. Smith, Jr. and I. Tager (2004). "Air pollution and cardiovascular disease: a statement for healthcare professionals from the Expert Panel on Population and Prevention Science of the American Heart Association." Circulation **109**(21): 2655-2671.

Brook, R. D., S. Rajagopalan, C. A. Pope, 3rd, J. R. Brook, A. Bhatnagar, A. V. Diez-Roux, F. Holguin, Y. Hong, R. V. Luepker, M. A. Mittleman, A. Peters, D. Siscovick, S. C. Smith, Jr., L. Whitsel and J. D. Kaufman (2010). "Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association." Circulation **121**(21): 2331-2378.

Brook, R. D., Z. Sun, J. R. Brook, X. Zhao, Y. Ruan, J. Yan, B. Mukherjee, X. Rao, F. Duan, L. Sun, R. Liang, H. Lian, S. Zhang, Q. Fang, D. Gu, Q. Sun, Z. Fan and S. Rajagopalan (2016). "Extreme Air Pollution Conditions Adversely Affect Blood Pressure and Insulin Resistance: The Air Pollution and Cardiometabolic Disease Study." Hypertension **67**(1): 77-85.

Brown, J. S., T. F. Bateson and W. F. McDonnell (2008). "Effects of exposure to 0.06 ppm ozone on FEV1 in humans: a secondary analysis of existing data." Environ Health Perspect **116**(8): 1023-1026.

Brunekreef, B., R. Beelen, G. Hoek, L. Schouten, S. Bausch-Goldbohm, P. Fischer, B. Armstrong, E. Hughes, M. Jerrett and P. van den Brandt. (2009). "Effects of long-term exposure to traffic-related air pollution on respiratory and cardiovascular mortality in the Netherlands: The NLCS-AIR Study." Boston, MA Health Effects Institute. from http://www.n65.nl/NCLS-AIR-Study-2009.pdf.

Brunekreef, B. and S. T. Holgate (2002). "Air pollution and health." Lancet **360**(9341): 1233-1242.

Cai, Y., B. Zhang, W. Ke, B. Feng, H. Lin, J. Xiao, W. Zeng, X. Li, J. Tao, Z. Yang, W. Ma and T. Liu (2016). "Associations of Short-Term and Long-Term Exposure to Ambient Air Pollutants With Hypertension: A Systematic Review and Meta-Analysis." Hypertension **68**(1): 62-70.

California Air Resources Board. (2010a). "Estimate of Premature Deaths Associated with Fine Particle Pollution (PM2.5) in California Using a U.S. Environmental Protection Agency Methodology."

California Air Resources Board. (2010b, February 25, 2010). "Rulemaking Identification of Particulate Emissions from Diesel-Fueled Engines as a Toxic Air Contaminant." Retrieved Oct 7, 2016, from https://www.arb.ca.gov/regact/diesltac/diesltac.htm.

California Air Resources Board and Office of Environmental Health Hazard Assessment. (2002). "Public Hearing to Consider Amendments to the Ambient Air Quality Standards for Particulate Matter and Sulfates." California Environmental Protection Agency. from http://arbis.arb.ca.gov/research/aaqs/std-rs/pm-final/pm-final.htm.

California Air Resources Board and Office of Environmental Health Hazard Assessment. (2005). "Review of the California Ambient Air Quality Standard for Ozone." California Air Resources Board and Office of Environmental Health Hazard Assessment. from http://www.arb.ca.gov/research/aaqs/ozone-rs/rev-staff/rev-staff.htm.

California Air Resources Board and Office of Environmental Health Hazard Assessment. (2007). "Review of the California Ambient Air Quality Standard for Nitrogen Dioxide." California Air Resources Board and Office of Environmental Health Hazard Assessment. from http://www.arb.ca.gov/research/aaqs/no2-rs/no2-doc.htm

Centers for Disease Control and Prevention. (2016, March 15, 2016). "What Do Parents Need to Know to Protect Their Children?" Retrieved May 31, 2016, from http://www.cdc.gov/nceh/lead/ACCLPP/blood_lead_levels.htm.

Chen, C., M. Arjomandi, J. Balmes, I. Tager and N. Holland (2007). "Effects of chronic and acute ozone exposure on lipid peroxidation and antioxidant capacity in healthy young adults." Environ Health Perspect **115**(12): 1732-1737.

Chen, L., P. J. Villeneuve, B. H. Rowe, L. Liu and D. M. Stieb (2014). "The Air Quality Health Index as a predictor of emergency department visits for ischemic stroke in Edmonton, Canada." Journal of Exposure Science and Environmental Epidemiology **24**(4): 358-364.

Chen, L. H., S. F. Knutsen, D. Shavlik, W. L. Beeson, F. Petersen, M. Ghamsary and D. Abbey (2005). "The association between fatal coronary heart disease and ambient particulate air pollution: Are females at greater risk?" Environ Health Perspect **113**(12): 1723-1729.

Cheng, C., M. Campbell, Q. Li, G. Li, H. Auld, N. Day, D. Pengelly, S. Gingrich, J. Klaassen, D. MacIver, N. Comer, Y. Mao, W. Thompson and H. Lin (2008). "Differential and combined impacts of extreme temperatures and air pollution on human mortality in south–central Canada. Part I: historical analysis." Air Qual Atmos Health **1**: 209-222.

Cho, A. K. (2016). "Quantitative assays in the characterization of ambient air." Diamond Bar, CA SCAQMD.

Coogan, P. F., L. F. White, M. Jerrett, R. D. Brook, J. G. Su, E. Seto, R. Burnett, J. R. Palmer and L. Rosenberg (2012). "Air pollution and incidence of hypertension and diabetes mellitus in black women living in Los Angeles." Circulation **125**(6): 767-772.

Correia, A. W., C. A. Pope, 3rd, D. W. Dockery, Y. Wang, M. Ezzati and F. Dominici (2013). "Effect of air pollution control on life expectancy in the United States: an analysis of 545 U.S. counties for the period from 2000 to 2007." Epidemiology **24**(1): 23-31.

Danysh, H. E., K. Zhang, L. E. Mitchell, M. E. Scheurer and P. J. Lupo (2016). "Maternal residential proximity to major roadways at delivery and childhood central nervous system tumors." Environ Res **146**: 315-322.

DeFranco, E., E. Hall, M. Hossain, A. Chen, E. N. Haynes, D. Jones, S. Ren, L. Lu and L. Muglia (2015). "Air pollution and stillbirth risk: exposure to airborne particulate matter during pregnancy is associated with fetal death." PLoS One **10**(3): e0120594.

Delamater, P. L., A. O. Finley and S. Banerjee (2012). "An analysis of asthma hospitalizations, air pollution, and weather conditions in Los Angeles County, California." Sci Total Environ **425**: 110-118.

Delfino, R. J., D. L. Gillen, T. Tjoa, N. Staimer, A. Polidori, M. Arhami, C. Sioutas and J. Longhurst (2011). "Electrocardiographic ST-segment depression and exposure to traffic-related aerosols in elderly subjects with coronary artery disease." Environmental Health Perspectives **119**(2): 196-202.

Delfino, R. J., H. Gong, Jr., W. S. Linn, E. D. Pellizzari and Y. Hu (2003). "Asthma symptoms in Hispanic children and daily ambient exposures to toxic and criteria air pollutants." Environ Health Perspect **111**(4): 647-656.

Delfino, R. J., T. Tjoa, D. L. Gillen, N. Staimer, A. Polidori, M. Arhami, L. Jamner, C. Sioutas and J. Longhurst (2010). "Traffic-related air pollution and blood pressure in elderly subjects with coronary artery disease." Epidemiology **21**(3): 396-404.

Delfino, R. J., J. Wu, T. Tjoa, S. K. Gullesserian, B. Nickerson and D. L. Gillen (2014). "Asthma morbidity and ambient air pollution: effect modification by residential traffic-related air pollution." Epidemiology **25**(1): 48-57.

Devlin, R. B., C. B. Smith, M. T. Schmitt, A. G. Rappold, A. Hinderliter, D. Graff and M. S. Carraway (2014). "Controlled exposure of humans with metabolic syndrome to concentrated ultrafine ambient particulate matter causes cardiovascular effects." Toxicol Sci **140**(1): 61-72.

Diez Roux, A. V., A. H. Auchincloss, T. G. Franklin, T. Raghunathan, R. G. Barr, J. Kaufman, B. Astor and J. Keeler (2008). "Long-term exposure to ambient particulate matter and prevalence of subclinical atherosclerosis in the Multi-Ethnic Study of Atherosclerosis." Am J Epidemiol **167**(6): 667-675.

Dockery, D. W., C. A. Pope, 3rd, X. Xu, J. D. Spengler, J. H. Ware, M. E. Fay, B. G. Ferris, Jr. and F. E. Speizer (1993). "An association between air pollution and mortality in six U.S. cities." N Engl J Med **329**(24): 1753-1759.

Dodge, D. E. and G. Harris. (2015). "The Air Toxics Hot Spots Program Guidance Manual for Preparation of Health Risk Assessments." Sacramento Office of Environmental Health Hazard Assessment. from http://oehha.ca.gov/media/downloads/crnr/2015guidancemanual.pdf.

Dominici, F., A. McDermott, S. L. Zeger and J. M. Samet (2002). "On the use of generalized additive models in time-series studies of air pollution and health." Am J Epidemiol **156**(3): 193-203.

Dominici, F., R. D. Peng, M. L. Bell, L. Pham, A. McDermott, S. L. Zeger and J. M. Samet (2006). "Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases." Jama **295**(10): 1127-1134.

Dominici, F., R. D. Peng, S. L. Zeger, R. H. White and J. M. Samet (2007). "Particulate air pollution and mortality in the United States: did the risks change from 1987 to 2000?" Am J Epidemiol **166**(8): 880-888.

Eckel, S. P., M. Cockburn, Y. H. Shu, H. Deng, F. W. Lurmann, L. Liu and F. D. Gilliland (2016). "Air pollution affects lung cancer survival." Thorax **71**(10): 891-898.

Eftim, S. E., J. M. Samet, H. Janes, A. McDermott and F. Dominici (2008). "Fine particulate matter and mortality: a comparison of the six cities and American Cancer Society cohorts with a medicare cohort." Epidemiology **19**(2): 209-216.

Eiguren-Fernandez, A., E. Di Stefano, D. A. Schmitz, A. L. Guarieiro, E. M. Salinas, E. Nasser, J. R. Froines and A. K. Cho (2015). "Chemical reactivities of ambient air samples in three Southern California communities." J Air Waste Manag Assoc **65**(3): 270-277.

Ensor, K. B., L. H. Raun and D. Persse (2013). "A case-crossover analysis of out-of-hospital cardiac arrest and air pollution." Circulation **127**(11): 1192-1199.

Enstrom, J. E. (2005). "Fine particulate air pollution and total mortality among elderly Californians, 1973-2002." Inhal Toxicol **17**(14): 803-816.

Evans, K. A., J. S. Halterman, P. K. Hopke, M. Fagnano and D. Q. Rich (2014). "Increased ultrafine particles and carbon monoxide concentrations are associated with asthma exacerbation among urban children." Environ Res **129**: 11-19.

Eze, I. C., E. Schaffner, M. Foraster, M. Imboden, A. von Eckardstein, M. W. Gerbase, T. Rothe, T. Rochat, N. Kunzli, C. Schindler and N. Probst-Hensch (2015). "Long-Term Exposure to Ambient Air Pollution and Metabolic Syndrome in Adults." PLoS One **10**(6): e0130337.

Fanning, E. W., J. R. Froines, M. J. Utell, M. Lippmann, G. Oberdorster, M. Frampton, J. Godleski and T. V. Larson (2009). "Particulate matter (PM) research centers (1999-2005) and the role of interdisciplinary center-based research." Environ Health Perspect **117**(2): 167-174.

Garcia, C. A., P. S. Yap, H. Y. Park and B. L. Weller (2016). "Association of long-term PM2.5 exposure with mortality using different air pollution exposure models: impacts in rural and urban California." Int J Environ Health Res **26**(2): 145-157.

Gatto, N. M., V. W. Henderson, H. N. Hodis, J. A. St John, F. Lurmann, J. C. Chen and W. J. Mack (2014). "Components of air pollution and cognitive function in middle-aged and older adults in Los Angeles." Neurotoxicology **40**: 1-7.

Gauderman, W. J., E. Avol, F. Gilliland, H. Vora, D. Thomas, K. Berhane, R. McConnell, N. Kuenzli, F. Lurmann, E. Rappaport, H. Margolis, D. Bates and J. Peters (2004). "The effect of air pollution on lung development from 10 to 18 years of age." N Engl J Med **351**(11): 1057-1067.

Gauderman, W. J., G. F. Gilliland, H. Vora, E. Avol, D. Stram, R. McConnell, D. Thomas, F. Lurmann, H. G. Margolis, E. B. Rappaport, K. Berhane and J. M. Peters (2002). "Association between air pollution and lung function growth in southern California children: results from a second cohort." Am J Respir Crit Care Med **166**(1): 76-84.

Gauderman, W. J., R. McConnell, F. Gilliland, S. London, D. Thomas, E. Avol, H. Vora, K. Berhane, E. B. Rappaport, F. Lurmann, H. G. Margolis and J. Peters (2000). "Association between air pollution and lung function growth in southern California children." Am J Respir Crit Care Med **162**(4 Pt 1): 1383-1390.

Gauderman, W. J., R. Urman, E. Avol, K. Berhane, R. McConnell, E. Rappaport, R. Chang, F. Lurmann and F. Gilliland (2015). "Association of improved air quality with lung development in children." N Engl J Med **372**(10): 905-913.

Gharibvand, L., D. Shavlik, M. Ghamsary, W. L. Beeson, S. Soret, R. Knutsen and S. F. Knutsen (2016). "The Association between Ambient Fine Particulate Air Pollution and Lung Cancer Incidence: Results from the AHSMOG-2 Study." Environ Health Perspect.

Ghosh, J. K., J. E. Heck, M. Cockburn, J. Su, M. Jerrett and B. Ritz (2013). "Prenatal exposure to traffic-related air pollution and risk of early childhood cancers." Am J Epidemiol **178**(8): 1233-1239.

Ghosh, J. K., M. Wilhelm, J. Su, D. Goldberg, M. Cockburn, M. Jerrett and B. Ritz (2012). "Assessing the influence of traffic-related air pollution on risk of term low birth weight on the basis of land-use-based regression models and measures of air toxics." Am J Epidemiol **175**(12): 1262-1274.

Gianicolo, E. A. L., C. Mangia, M. Cervino, A. Bruni, M. G. Andreassi and G. Latini (2014). "Congenital anomalies among live births in a high environmental risk area-A case-control study in Brindisi (southern Italy)." Environmental Research **128**: 9-14.

Gilliland, F. D., K. Berhane, E. B. Rappaport, D. C. Thomas, E. Avol, W. J. Gauderman, S. J. London, H. G. Margolis, R. McConnell, K. T. Islam and J. M. Peters (2001). "The effects of ambient air pollution on school absenteeism due to respiratory illnesses." Epidemiology **12**(1): 43-54.

Green, R., V. Sarovar, B. Malig and R. Basu (2015). "Association of stillbirth with ambient air pollution in a California cohort study." Am J Epidemiol **181**(11): 874-882.

Greenberg, M. I., J. A. Curtis and D. Vearrier (2013). "The perception of odor is not a surrogate marker for chemical exposure: a review of factors influencing human odor perception." Clin Toxicol (Phila) **51**(2): 70-76.

Greer, J. R., D. E. Abbey and R. J. Burchette (1993). "Asthma related to occupational and ambient air pollutants in nonsmokers." J Occup Med **35**(9): 909-915.

Guarnieri, M. and J. R. Balmes (2014). "Outdoor air pollution and asthma." Lancet **383**(9928): 1581-1592.

Hales, N. M., C. C. Barton, M. R. Ransom, R. T. Allen and C. A. Pope, 3rd (2016). "A Quasi-Experimental Analysis of Elementary School Absences and Fine Particulate Air Pollution." Medicine (Baltimore) **95**(9): e2916.

Hamra, G. B., N. Guha, A. Cohen, F. Laden, O. Raaschou-Nielsen, J. M. Samet, P. Vineis, F. Forastiere, P. Saldiva, T. Yorifuji and D. Loomis (2014). "Outdoor particulate matter exposure and lung cancer: a systematic review and meta-analysis." Environ Health Perspect **122**(9): 906-911.

Harley, R. (2014). "On-Road Measurement of Emissions from Heavy-Duty Diesel Trucks: Impacts of Fleet Turnover and ARB's Drayage Truck Regulation, Final Report." Sacramento, CA California Air Resources Board. Contract No. 09-340.

Harris, M. H., D. R. Gold, S. L. Rifas-Shiman, S. J. Melly, A. Zanobetti, B. A. Coull, J. D. Schwartz, A. Gryparis, I. Kloog, P. Koutrakis, D. C. Bellinger, R. F. White, S. K. Sagiv and E. Oken (2015). "Prenatal and Childhood Traffic-Related Pollution Exposure and Childhood Cognition in the Project Viva Cohort (Massachusetts, USA)." Environ Health Perspect **123**(10): 1072-1078.

Hart, C. L., G. D. Smith, D. J. Hole and V. M. Hawthorne (2006). "Carboxyhaemoglobin concentration, smoking habit, and mortality in 25 years in the Renfrew/Paisley prospective cohort study." Heart **92**(3): 321-324.

Hart, J. E., S. E. Chiuve, F. Laden and C. M. Albert (2014). "Roadway proximity and risk of sudden cardiac death in women." Circulation **130**(17): 1474-1482.

Hart, J. E., E. Garshick, D. W. Dockery, T. J. Smith, L. Ryan and F. Laden (2011). "Long-term ambient multi-pollutant exposures and mortality." American Journal of Respiratory and Critical Care Medicine **183**(1): 73-78.

Health Effects Institute. (2003). "Revised Analyses of the National Morbidity, Mortality, and Air Pollution Study, Part II. Revised Analyses of Time-Series Studies of Air Pollution and Health." Boston, MA Health Effects Institute.

Heaney, C. D., S. Wing, R. L. Campbell, D. Caldwell, B. Hopkins, D. Richardson and K. Yeatts (2011). "Relation between malodor, ambient hydrogen sulfide, and health in a community bordering a landfill." Environ Res **111**(6): 847-852.

HEI Review Panel on Ultrafine Particles. (2013). "Understanding the Health Effects of Ambient Ultrafine Particles." HEI Perspectives Boston, MA Health Effects Institute.

Hooiveld, M., C. van Dijk, F. van der Sman-de Beer, L. A. Smit, M. Vogelaar, I. M. Wouters, D. J. Heederik and C. J. Yzermans (2015). "Odour annoyance in the neighbourhood of livestock farming - perceived health and health care seeking behaviour." Ann Agric Environ Med **22**(1): 55-61.

Horstman, D. H., B. A. Ball, J. Brown, T. Gerrity and L. J. Folinsbee (1995). "Comparison of pulmonary responses of asthmatic and nonasthmatic subjects performing light exercise while exposed to a low level of ozone." Toxicology and Industrial Health **11**(4): 369-385.

Horstman, D. H., L. J. Folinsbee, P. J. Ives, S. Abdul-Salaam and W. F. McDonnell (1990). "Ozone concentration and pulmonary response relationships for 6.6-hour exposures with five hours of moderate exercise to 0.08, 0.10, and 0.12 ppm." Am Rev Respir Dis **142**(5): 1158-1163.

Huang, P. L. (2009). "A comprehensive definition for metabolic syndrome." Dis Model Mech **2**(5-6): 231-237.

Huang, Y., F. Dominici and M. L. Bell (2005). "Bayesian hierarchical distributed lag models for summer ozone exposure and cardio-respiratory mortality." Environmetrics **16**(5): 547-562.

Hwang, B. F., Y. L. Lee and J. J. Jaakkola (2011). "Air pollution and stillbirth: a population-based case-control study in Taiwan." Environ Health Perspect **119**(9): 1345-1349.

Industrial Economics Inc. (2016a). "Literature Review of Air Pollution-Related Health Endpoints and Concentration-Response Functions for Ozone, Nitrogen Dioxide, and Sulfur Dioxide: Results and Recommendations (Final Report)." Cambridge, MA Industrial Economics, Incorporated. from http://www.aqmd.gov/docs/default-source/clean-air-plans/socioeconomic-analysis/iec_gasplitreview_092916.pdf?sfvrsn=2.

Industrial Economics Inc. (2016b). "Literature Review of Air Pollution-Related Health Endpoints and Concentration-Response Functions for Particulate Matter: Results and Recommendations (Final Report)." Cambridge, MA Industrial Economics, Incorporated. from http://www.aqmd.gov/docs/default-source/clean-air-plans/socioeconomic-analysis/iec_pmlitreview_092916.pdf?sfvrsn=2.

International Agency for Research on Cancer. (1989). "Diesel and Gasoline Engines Exhaust and Some Nitroarenes." IARC Monographs of the Evaluation of Carcinogenic Risk to Humans Lyon, France International Agency for Research on Cancer. Volume 46.

International Agency for Research on Cancer. (2012a). "Chemical Agents and Related Occupations." IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Lyon, France International Agency for Research on Cancer. 100F, from http://monographs.iarc.fr/ENG/Monographs/vol100F/index.php.

International Agency for Research on Cancer. (2012b). "Diesel and Gasoline Engines Exhaust and Some Nitroarenes." IARC Monographs of the Evaluation of Carcinogenic Risk to Humans Lyon, France International Agency for Research on Cancer. 105.

International Agency for Research on Cancer. (2015). "Outdoor Air Pollution." IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Lyon, France International Agency for Research on Cancer. 109.

Islam, T., K. Berhane, R. McConnell, W. J. Gauderman, E. Avol, J. M. Peters and F. D. Gilliland (2009). "Glutathione-S-transferase (GST) P1, GSTM1, exercise, ozone and asthma incidence in school children." Thorax **64**(3): 197-202.

Islam, T., W. J. Gauderman, K. Berhane, R. McConnell, E. Avol, J. M. Peters and F. D. Gilliland (2007). "Relationship between air pollution, lung function and asthma in adolescents." Thorax **62**(11): 957-963.

Islam, T., R. McConnell, W. J. Gauderman, E. Avol, J. M. Peters and F. D. Gilliland (2008). "Ozone, oxidant defense genes, and risk of asthma during adolescence." Am J Respir Crit Care Med **177**(4): 388-395.

Ito, K., S. F. De Leon and M. Lippmann (2005). "Associations between ozone and daily mortality: analysis and meta-analysis." Epidemiology **16**(4): 446-457.

Jacquemin, B., F. Kauffmann, I. Pin, N. Le Moual, J. Bousquet, F. Gormand, J. Just, R. Nadif, C. Pison, D. Vervloet, N. Kunzli and V. Siroux (2012). "Air pollution and asthma control in the Epidemiological study on the Genetics and Environment of Asthma." J Epidemiol Community Health **66**(9): 796-802.

Jerrett, M., R. T. Burnett, B. S. Beckerman, M. C. Turner, D. Krewski, G. Thurston, R. V. Martin, A. van Donkelaar, E. Hughes, Y. Shi, S. M. Gapstur, M. J. Thun and C. A. Pope, 3rd (2013). "Spatial analysis of air pollution and mortality in California." Am J Respir Crit Care Med **188**(5): 593-599.

Jerrett, M., R. T. Burnett, R. Ma, C. A. Pope, 3rd, D. Krewski, K. B. Newbold, G. Thurston, Y. Shi, N. Finkelstein, E. E. Calle and M. J. Thun (2005). "Spatial analysis of air pollution and mortality in Los Angeles." Epidemiology **16**(6): 727-736.

Jerrett, M., R. T. Burnett, C. A. Pope, 3rd, K. Ito, G. Thurston, D. Krewski, Y. Shi, E. Calle and M. Thun (2009). "Long-term ozone exposure and mortality." N Engl J Med **360**(11): 1085-1095.

Jerrett, M., K. Shankardass, K. Berhane, W. J. Gauderman, N. Kunzli, E. Avol, F. Gilliland, F. Lurmann, J. N. Molitor, J. T. Molitor, D. C. Thomas, J. Peters and R. McConnell (2008). "Traffic-related air pollution and asthma onset in children: a prospective cohort study with individual exposure measurement." Environ Health Perspect **116**(10): 1433-1438.

Johnston, R. A., J. P. Mizgerd, L. Flynt, L. J. Quinton, E. S. Williams and S. A. Shore (2007). "Type I interleukin-1 receptor is required for pulmonary responses to subacute ozone exposure in mice." Am J Respir Cell Mol Biol **37**(4): 477-484.

Kaiser, J. (1997). "Getting a handle on air pollution's tiny killers." Science **276**(5309): 33.

Kang, X., N. Li, M. Wang, P. Boontheung, C. Sioutas, J. R. Harkema, L. A. Bramble, A. E. Nel and J. A. Loo (2010). "Adjuvant effects of ambient particulate matter monitored by proteomics of bronchoalveolar lavage fluid." Proteomics **10**(3): 520-531.

Karottki, D. G., G. Beko, G. Clausen, A. M. Madsen, Z. J. Andersen, A. Massling, M. Ketzel, T. Ellermann, R. Lund, T. Sigsgaard, P. Moller and S. Loft (2014). "Cardiovascular and lung function in relation to outdoor and indoor exposure to fine and ultrafine particulate matter in middle-aged subjects." Environ Int **73**: 372-381.

Karr, C., T. Lumley, A. Schreuder, R. Davis, T. Larson, B. Ritz and J. Kaufman (2007). "Effects of subchronic and chronic exposure to ambient air pollutants on infant bronchiolitis." Am J Epidemiol **165**(5): 553-560.

Katsouyanni, K., J. M. Samet, H. R. Anderson, R. Atkinson, A. Le Tertre, S. Medina, E. Samoli, G. Touloumi, R. T. Burnett, D. Krewski, T. Ramsay, F. Dominici, R. D. Peng, J. Schwartz and A. Zanobetti (2009). "Air pollution and health: a European and North American approach (APHENA)." Res Rep Health Eff Inst(142): 5-90.

Kehrl, H. R., M. J. Hazucha, J. J. Solic and P. A. Bromberg (1985). "Responses of subjects with chronic obstructive pulmonary disease after exposures to 0.3 ppm ozone." American Review of Respiratory Disease **131**(5): 719-724.

Khalek, I. A., T. L. Bougher and P. M. Merritt. (2009). "Phase I of the Advanced Collaborative Emissions Study (Final Report)."   Alpharetta, GA Coordinating Research Council, Inc. SwRI® Project No. 03.13062, from

https://www.healtheffects.org/publication/executive-summary-advanced-collaborative-emissions-study-aces.

Kim, C. S., N. E. Alexis, A. G. Rappold, H. Kehrl, M. J. Hazucha, J. C. Lay, M. T. Schmitt, M. Case, R. B. Devlin, D. B. Peden and D. Diaz-Sanchez (2011). "Lung function and inflammatory responses in healthy young adults exposed to 0.06 ppm ozone for 6.6 hours." Am J Respir Crit Care Med **183**(9): 1215-1221.

Kingsley, S. L., M. N. Eliot, E. A. Whitsel, Y. Wang, B. A. Coull, L. Hou, H. G. Margolis, K. L. Margolis, L. Mu, W. C. Wu, K. C. Johnson, M. A. Allison, J. E. Manson, C. B. Eaton and G. A. Wellenius (2015). "Residential proximity to major roadways and incident hypertension in post-menopausal women." Environ Res **142**: 522-528.

Koken, P. J., W. T. Piver, F. Ye, A. Elixhauser, L. M. Olsen and C. J. Portier (2003). "Temperature, air pollution, and hospitalization for cardiovascular diseases among elderly people in Denver." Environ Health Perspect **111**(10): 1312-1317.

Kreit, J. W., K. B. Gross, T. B. Moore, T. J. Lorenzen, J. D'Arcy and W. L. Eschenbacher (1989). "Ozone-induced changes in pulmonary function and bronchial responsiveness in asthmatics." Journal of Applied Physiology **66**(1): 217-222.

Krewski, D., M. Jerrett, R. T. Burnett, R. Ma, E. Hughes, Y. Shi, M. C. Turner, C. A. Pope, 3rd, G. Thurston, E. E. Calle, M. J. Thun, B. Beckerman, P. DeLuca, N. Finkelstein, K. Ito, D. K. Moore, K. B. Newbold, T. Ramsay, Z. Ross, H. Shin and B. Tempalski (2009). "Extended follow-up and spatial analysis of the American Cancer Society study linking particulate air pollution and mortality." Res Rep Health Eff Inst(140): 5-114; discussion 115-136.

Krewski, D. B., R.T.; Goldberg, M.S.; Hoover, K.; Siemiatycki, J.; Jerrett, M.; Abrahamowicz, M.; White, W.H. (2000). "Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of Particulate Air Pollution and Mortality." Cambridge, MA Health Effects Institute.

Kunzli, N., P. O. Bridevaux, L. J. Liu, R. Garcia-Esteban, C. Schindler, M. W. Gerbase, J. Sunyer, D. Keidel and T. Rochat (2009). "Traffic-related air pollution correlates with adult-onset asthma among never-smokers." Thorax **64**(8): 664-670.

Kunzli, N., M. Jerrett, W. J. Mack, B. Beckerman, L. LaBree, F. Gilliland, D. Thomas, J. Peters and H. N. Hodis (2005). "Ambient air pollution and atherosclerosis in Los Angeles." Environ Health Perspect **113**(2): 201-206.

Laden, F., J. Schwartz, F. E. Speizer and D. W. Dockery (2006). "Reduction in fine particulate air pollution and mortality: Extended follow-up of the Harvard Six Cities study." Am J Respir Crit Care Med **173**(6): 667-672.

Laurent, O., J. Hu, L. Li, M. Cockburn, L. Escobedo, M. J. Kleeman and J. Wu (2014). "Sources and contents of air pollution affecting term low birth weight in Los Angeles County, California, 2001-2008." Environ Res **134**: 488-495.

Lee, Y. L., R. McConnell, K. Berhane and F. D. Gilliland (2009). "Ambient ozone modifies the effect of tumor necrosis factor G-308A on bronchitic symptoms among children with asthma." Allergy **64**(9): 1342-1348.

Lepeule, J., F. Laden, D. Dockery and J. Schwartz (2012). "Chronic exposure to fine particles and mortality: an extended follow-up of the Harvard Six Cities study from 1974 to 2009." Environ Health Perspect **120**(7): 965-970.

Levy, J. I., S. M. Chemerynski and J. A. Sarnat (2005). "Ozone exposure and mortality: an empiric bayes metaregression analysis." Epidemiology **16**(4): 458-468.

Li, N., S. Georas, N. Alexis, P. Fritz, T. Xia, M. A. Williams, E. Horner and A. Nel (2016). "A work group report on ultrafine particles (American Academy of Allergy, Asthma & Immunology): Why ambient ultrafine and engineered nanoparticles should receive special attention for possible adverse health outcomes in human subjects." J Allergy Clin Immunol **138**(2): 386-396.

Li, N., J. R. Harkema, R. P. Lewandowski, M. Wang, L. A. Bramble, G. R. Gookin, Z. Ning, M. T. Kleinman, C. Sioutas and A. E. Nel (2010). "Ambient ultrafine particles provide a strong adjuvant effect in the secondary immune response: implication for traffic-related asthma flares." Am J Physiol Lung Cell Mol Physiol **299**(3): L374-383.

Li, N., M. Wang, L. A. Bramble, D. A. Schmitz, J. J. Schauer, C. Sioutas, J. R. Harkema and A. E. Nel (2009). "The adjuvant effect of ambient particulate matter is closely reflected by the particulate oxidant potential." Environ Health Perspect **117**(7): 1116-1123.

Linn, W. S., E. L. Avol, D. A. Shamoo, R. C. Peng, L. M. Valencia, D. E. Little and J. D. Hackney (1988). "Repeated laboratory ozone exposures of volunteer Los Angeles residents: an apparent seasonal variation in response." Toxicol Ind Health **4**(4): 505-520.

Linn, W. S., D. A. Fischer, D. A. Medway, U. T. Anzar, C. E. Spier, L. M. Valencia, T. G. Venet and J. D. Hackney (1982). "Short-term respiratory effects of 0.12 ppm ozone exposure in volunteers with chronic obstructive pulmonary disease." American Review of Respiratory Disease **125**(6): 658-663.

Linn, W. S., D. A. Shamoo, T. G. Venet, C. E. Spier, L. M. Valencia, U. T. Anzar and J. D. Hackney (1983). "Response to ozone in volunteers with chronic obstructive pulmonary disease." Archives of Environmental and Occupational Health **38**(5): 278-283.

Linn, W. S., Y. Szlachcic, H. Gong, Jr., P. L. Kinney and K. T. Berhane (2000). "Air pollution and daily hospital admissions in metropolitan Los Angeles." Environmental Health Perspectives **108**(5): 427-434.

Lipfert, F. W., J. D. Baty, J. P. Miller and R. E. Wyzga (2006). "PM2.5 constituents and related air quality variables as predictors of survival in a cohort of U.S. military veterans." Inhal Toxicol **18**(9): 645-657.

Lippmann, M. (2014). "Toxicological and epidemiological studies of cardiovascular effects of ambient air fine particulate matter (PM2.5) and its chemical components: coherence and public health implications." Crit Rev Toxicol **44**(4): 299-347.

Lipsett, M. J., B. D. Ostro, P. Reynolds, D. Goldberg, A. Hertz, M. Jerrett, D. F. Smith, C. Garcia, E. T. Chang and L. Bernstein (2011). "Long-term exposure to air pollution and cardiorespiratory disease in the California teachers study cohort." Am J Respir Crit Care Med **184**(7): 828-835.

Lu, F., L. Zhou, Y. Xu, T. Zheng, Y. Guo, G. A. Wellenius, B. A. Bassig, X. Chen, H. Wang and X. Zheng (2015). "Short-term effects of air pollution on daily mortality and years of life lost in Nanjing, China." Sci Total Environ **536**: 123-129.

Malig, B. J., D. L. Pearson, Y. B. Chang, R. Broadwin, R. Basu, R. S. Green and B. Ostro (2016). "A Time-Stratified Case-Crossover Study of Ambient Ozone Exposure and Emergency Department Visits for Specific Respiratory Diagnoses in California (2005-2008)." Environ Health Perspect **124**(6): 745-753.

McConnell, R., K. Berhane, F. Gilliland, S. J. London, T. Islam, W. J. Gauderman, E. Avol, H. G. Margolis and J. M. Peters (2002). "Asthma in exercising children exposed to ozone: a cohort study." Lancet **359**(9304): 386-391.

McConnell, R., K. Berhane, F. Gilliland, S. J. London, H. Vora, E. Avol, W. J. Gauderman, H. G. Margolis, F. Lurmann, D. C. Thomas and J. M. Peters (1999). "Air pollution and bronchitic symptoms in Southern California children with asthma." Environ Health Perspect **107**(9): 757-760.

McConnell, R., K. Berhane, F. Gilliland, J. Molitor, D. Thomas, F. Lurmann, E. Avol, W. J. Gauderman and J. M. Peters (2003). "Prospective study of air pollution and bronchitic symptoms in children with asthma." Am J Respir Crit Care Med **168**(7): 790-797.

McConnell, R., T. Islam, K. Shankardass, M. Jerrett, F. Lurmann, F. Gilliland, J. Gauderman, E. Avol, N. Kunzli, L. Yao, J. Peters and K. Berhane (2010). "Childhood incident asthma and traffic-related air pollution at home and school." Environ Health Perspect **118**(7): 1021-1026.

McDonald, J. D., J. C. Bemis, L. M. Hallberg and D. J. Conklin. (2015). "Advanced Collaborative Emissions Study (ACES): Lifetime Cancer and Non-Cancer Assessment in Rats Exposed to New-Technology Diesel Exhaust." Boston, MA Health Effects Institute. from https://www.healtheffects.org/publication/executive-summary-advanced-collaborative-emissions-study-aces.

McDonnell, W. F., D. E. Abbey, N. Nishino and M. D. Lebowitz (1999). "Long-term ambient ozone concentration and the incidence of asthma in nonsmoking adults: the AHSMOG Study." Environ Res **80**(2 Pt 1): 110-121.

McDonnell, W. F., N. Nishino-Ishikawa, F. F. Petersen, L. H. Chen and D. E. Abbey (2000). "Relationships of mortality with the fine and coarse fractions of long-term ambient PM10 concentrations in nonsmokers." J Expo Anal Environ Epidemiol **10**(5): 427-436.

Meng, Y. Y., R. P. Rull, M. Wilhelm, C. Lombardi, J. Balmes and B. Ritz (2010). "Outdoor air pollution and uncontrolled asthma in the San Joaquin Valley, California." J Epidemiol Community Health **64**(2): 142-147.

Meng, Y. Y., M. Wilhelm, R. P. Rull, P. English and B. Ritz (2007). "Traffic and outdoor air pollution levels near residences and poorly controlled asthma in adults." Ann Allergy Asthma Immunol **98**(5): 455-463.

Miller, K. A., D. S. Siscovick, L. Sheppard, K. Shepherd, J. H. Sullivan, G. L. Anderson and J. D. Kaufman (2007). "Long-term exposure to air pollution and incidence of cardiovascular events in women." N Engl J Med **356**(5): 447-458.

Mills, N. L., M. R. Miller, A. J. Lucking, J. Beveridge, L. Flint, A. J. Boere, P. H. Fokkens, N. A. Boon, T. Sandstrom, A. Blomberg, R. Duffin, K. Donaldson, P. W. Hadoke, F. R. Cassee and D. E. Newby (2011). "Combustion-derived nanoparticulate induces the adverse vascular effects of diesel exhaust inhalation." Eur Heart J **32**(21): 2660-2671.

Milojevic, A., P. Wilkinson, B. Armstrong, K. Bhaskaran, L. Smeeth and S. Hajat (2014). "Short-term effects of air pollution on a range of cardiovascular events in England and Wales: case-crossover analysis of the MINAP database, hospital admissions and mortality." Heart **100**(14): 1093-1098.

Mobasher, Z., M. T. Salam, T. M. Goodwin, F. Lurmann, S. A. Ingles and M. L. Wilson (2013). "Associations between ambient air pollution and Hypertensive Disorders of Pregnancy." Environ Res **123**: 9-16.

Moore, K., R. Neugebauer, F. Lurmann, J. Hall, V. Brajer, S. Alcorn and I. Tager (2008). "Ambient ozone concentrations cause increased hospitalizations for asthma in children: an 18-year study in Southern California." Environ Health Perspect **116**(8): 1063-1070.

Morello-Frosch, R., B. M. Jesdale, J. L. Sadd and M. Pastor (2010). "Ambient air pollution exposure and full-term birth weight in California." Environ Health **9**: 44.

Moridi, M., S. Ziaei and A. Kazemnejad (2014). "Exposure to ambient air pollutants and spontaneous abortion." Journal of Obstetrics and Gynaecology Research **40**(3): 743-748.

Nishimura, K. K., J. M. Galanter, L. A. Roth, S. S. Oh, N. Thakur, E. A. Nguyen, S. Thyne, H. J. Farber, D. Serebrisky, R. Kumar, E. Brigino-Buenaventura, A. Davis, M. A. LeNoir, K. Meade, W. Rodriguez-Cintron, P. C. Avila, L. N. Borrell, K. Bibbins-Domingo, J. R. Rodriguez-Santana, S. Sen, F. Lurmann, J. R. Balmes and E. G. Burchard (2013). "Early-life air pollution and asthma risk in minority children. The GALA II and SAGE II studies." Am J Respir Crit Care Med **188**(3): 309-318.

Oberdorster, G., R. M. Gelein, J. Ferin and B. Weiss (1995). "Association of particulate air pollution and acute mortality: involvement of ultrafine particles?" Inhal Toxicol **7**(1): 111-124.

Olsen, Y., D. G. Karottki, D. M. Jensen, G. Beko, B. U. Kjeldsen, G. Clausen, L. G. Hersoug, G. J. Holst, A. Wierzbicka, T. Sigsgaard, A. Linneberg, P. Moller and S. Loft (2014). "Vascular and lung function related to ultrafine and fine particles exposure assessed by personal and indoor monitoring: a cross-sectional study." Environ Health **13**: 112.

Ostro, B. (1987). "Air pollution and morbidity revisited: A specification test." Journal of Environmental Economics and Management **14**(1): 87-98.

Ostro, B., J. Hu, D. Goldberg, P. Reynolds, A. Hertz, L. Bernstein and M. J. Kleeman (2015). "Associations of mortality with long-term exposures to fine and ultrafine particles, species and sources: results from the California Teachers Study Cohort." Environ Health Perspect **123**(6): 549-556.

Ostro, B., M. Lipsett, P. Reynolds, D. Goldberg, A. Hertz, C. Garcia, K. D. Henderson and L. Bernstein (2010). "Long-term exposure to constituents of fine particulate air pollution and mortality: results from the California Teachers Study." Environ Health Perspect **118**(3): 363-369.

Ostro, B. D. (1990). "Associations between morbidity and alternative measures of particulate matter." Risk Anal **10**(3): 421-427.

Oudin, A., B. Forsberg, A. N. Adolfsson, N. Lind, L. Modig, M. Nordin, S. Nordin, R. Adolfsson and L. G. Nilsson (2016). "Traffic-Related Air Pollution and Dementia Incidence in Northern Sweden: A Longitudinal Study." Environ Health Perspect **124**(3): 306-312.

Padula, A. M., K. M. Mortimer, I. B. Tager, S. K. Hammond, F. W. Lurmann, W. Yang, D. K. Stevenson and G. M. Shaw (2014). "Traffic-related air pollution and risk of preterm birth in the San Joaquin Valley of California." Ann Epidemiol **24**(12): 888-895e884.

Padula, A. M., I. B. Tager, S. L. Carmichael, S. K. Hammond, F. Lurmann and G. M. Shaw (2013a). "The association of ambient air pollution and traffic exposures with selected congenital anomalies in the San Joaquin Valley of California." Am J Epidemiol **177**(10): 1074-1085.

Padula, A. M., I. B. Tager, S. L. Carmichael, S. K. Hammond, W. Yang, F. Lurmann and G. M. Shaw (2013b). "Ambient air pollution and traffic exposures and congenital heart defects in the San Joaquin Valley of California." Paediatr Perinat Epidemiol **27**(4): 329-339.

Padula, A. M., I. B. Tager, S. L. Carmichael, S. K. Hammond, W. Yang, F. W. Lurmann and G. M. Shaw (2013c). "Traffic-related air pollution and selected birth defects in the San Joaquin Valley of California." Birth Defects Res A Clin Mol Teratol **97**(11): 730-735.

Padula, A. M., W. Yang, S. L. Carmichael, I. B. Tager, F. Lurmann, S. K. Hammond and G. M. Shaw (2015). "Air Pollution, Neighbourhood Socioeconomic Factors, and Neural Tube Defects in the San Joaquin Valley of California." Paediatr Perinat Epidemiol **29**(6): 536-545.

Park, H., B. Lee, E. H. Ha, J. T. Lee, H. Kim and Y. C. Hong (2002). "Association of air pollution with school absenteeism due to illness." Arch Pediatr Adolesc Med **156**(12): 1235-1239.

Parker, J. D., T. J. Woodruff, R. Basu and K. C. Schoendorf (2005). "Air pollution and birth weight among term infants in California." Pediatrics **115**(1): 121-128.

Pascal, L., M. Pascal, M. Stempfelet, S. Goria and C. Declercq (2013). "Ecological study on hospitalizations for cancer, cardiovascular, and respiratory diseases in the industrial area of Etang-de-Berre in the South of France." Journal of Environmental and Public Health **2013**: 328737.

Peters, A., B. Veronesi, L. Calderon-Garciduenas, P. Gehr, L. C. Chen, M. Geiser, W. Reed, B. Rothen-Rutishauser, S. Schurch and H. Schulz (2006). "Translocation and potential neurological effects of fine and ultrafine particles a critical update." Part Fibre Toxicol **3**: 13.

Pope, C. A., 3rd, R. T. Burnett, M. J. Thun, E. E. Calle, D. Krewski, K. Ito and G. D. Thurston (2002). "Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution." Jama **287**(9): 1132-1141.

Pope, C. A., 3rd and D. W. Dockery (2006). "Health effects of fine particulate air pollution: lines that connect." J Air Waste Manag Assoc **56**(6): 709-742.

Pope, C. A., 3rd, M. Ezzati and D. W. Dockery (2013). "Fine particulate air pollution and life expectancies in the United States: the role of influential observations." J Air Waste Manag Assoc **63**(2): 129-132.

Pope, C. A., 3rd, M. J. Thun, M. M. Namboodiri, D. W. Dockery, J. S. Evans, F. E. Speizer and C. W. Heath, Jr. (1995). "Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults." Am J Respir Crit Care Med **151**(3 Pt 1): 669-674.

Pope, C. A., 3rd, M. C. Turner, R. T. Burnett, M. Jerrett, S. M. Gapstur, W. R. Diver, D. Krewski and R. D. Brook (2015). "Relationships between fine particulate air pollution, cardiometabolic disorders, and cardiovascular mortality." Circ Res **116**(1): 108-115.

Power, M. C., M. G. Weisskopf, S. E. Alexeeff, B. A. Coull, A. Spiro, 3rd and J. Schwartz (2011). "Traffic-related air pollution and cognitive function in a cohort of older men." Environ Health Perspect **119**(5): 682-687.

Puett, R. C., J. Schwartz, J. E. Hart, J. D. Yanosky, F. E. Speizer, H. Suh, C. J. Paciorek, L. M. Neas and F. Laden (2008). "Chronic particulate exposure, mortality, and coronary heart disease in the nurses' health study." Am J Epidemiol **168**(10): 1161-1168.

Ransom, M. R. and C. A. Pope, 3rd (1992). "Elementary school absences and PM10 pollution in Utah Valley." Environ Res **58**(2): 204-219.

Raz, R., A. L. Roberts, K. Lyall, J. E. Hart, A. C. Just, F. Laden and M. G. Weisskopf (2015). "Autism spectrum disorder and particulate matter air pollution before, during, and after pregnancy: a nested case-control analysis within the Nurses' Health Study II Cohort." Environ Health Perspect **123**(3): 264-270.

Reiss, R., E. L. Anderson, C. E. Cross, G. Hidy, D. Hoel, R. McClellan and S. Moolgavkar (2007). "Evidence of health impacts of sulfate-and nitrate-containing particles in ambient air." Inhal Toxicol **19**(5): 419-449.

Rice, M. B., P. L. Ljungman, E. H. Wilker, K. S. Dorans, D. R. Gold, J. Schwartz, P. Koutrakis, G. R. Washko, G. T. O'Connor and M. A. Mittleman (2015). "Long-term exposure to traffic emissions and fine particulate matter and lung function decline in the Framingham heart study." Am J Respir Crit Care Med **191**(6): 656-664.

Rich, D. Q., K. Liu, J. Zhang, S. W. Thurston, T. P. Stevens, Y. Pan, C. Kane, B. Weinberger, P. Ohman-Strickland, T. J. Woodruff, X. Duan, V. Assibey-Mensah and J. Zhang (2015). "Differences in birth weight associated with the 2008 Beijing olympic air pollution reduction: results from a natural experiment." Environmental Health Perspectives **123**(9): 880-887.

Ritz, B., P. C. Lee, J. Hansen, C. F. Lassen, M. Ketzel, M. Sorensen and O. Raaschou-Nielsen (2016). "Traffic-Related Air Pollution and Parkinson's Disease in Denmark: A Case-Control Study." Environ Health Perspect **124**(3): 351-356.

Ritz, B., J. Qiu, P. C. Lee, F. Lurmann, B. Penfold, R. Erin Weiss, R. McConnell, C. Arora, C. Hobel and M. Wilhelm (2014). "Prenatal air pollution exposure and ultrasound measures of fetal growth in Los Angeles, California." Environmental Research **130**: 7-13.

Ritz, B., M. Wilhelm, K. J. Hoggatt and J. K. Ghosh (2007). "Ambient air pollution and preterm birth in the environment and pregnancy outcomes study at the University of California, Los Angeles." Am J Epidemiol **166**(9): 1045-1052.

Ritz, B., M. Wilhelm and Y. Zhao (2006). "Air pollution and infant death in southern California, 1989-2000." Pediatrics **118**(2): 493-502.

Ritz, B., F. Yu, G. Chapa and S. Fruin (2000). "Effect of air pollution on preterm birth among children born in Southern California between 1989 and 1993." Epidemiology **11**(5): 502-511.

Ritz, B., F. Yu, S. Fruin, G. Chapa, G. M. Shaw and J. A. Harris (2002). "Ambient air pollution and risk of birth defects in Southern California." Am J Epidemiol **155**(1): 17-25.

Robledo, C. A., P. Mendola, E. Yeung, T. Mannisto, R. Sundaram, D. Liu, Q. Ying, S. Sherman and K. L. Grantz (2015). "Preconception and early pregnancy air pollution exposures and risk of gestational diabetes mellitus." Environ Res **137**: 316-322.

Rodopoulou, S., M. C. Chalbot, E. Samoli, D. W. Dubois, B. D. San Filippo and I. G. Kavouras (2014). "Air pollution and hospital emergency room and admissions for cardiovascular and respiratory diseases in Dona Ana County, New Mexico." Environ Res **129**: 39-46.

Romieu, I., N. Gouveia, L. A. Cifuentes, A. P. de Leon, W. Junger, J. Vera, V. Strappa, M. Hurtado-Diaz, V. Miranda-Soberanis, L. Rojas-Bracho, L. Carbajal-Arroyo and G. Tzintzun-Cervantes (2012). "Multicity study of air pollution and mortality in Latin America (the ESCALA study)." Res Rep Health Eff Inst(171): 5-86.

Salam, M. T., T. Islam, W. J. Gauderman and F. D. Gilliland (2009). "Roles of arginase variants, atopy, and ozone in childhood asthma." J Allergy Clin Immunol **123**(3): 596-602, 602.e591-598.

Salam, M. T., J. Millstein, Y. F. Li, F. W. Lurmann, H. G. Margolis and F. D. Gilliland (2005). "Birth outcomes and prenatal exposure to ozone, carbon monoxide, and particulate matter: results from the Children's Health Study." Environ Health Perspect **113**(11): 1638-1644.

Samet, J. M., F. Dominici, F. C. Curriero, I. Coursac and S. L. Zeger (2000a). "Fine particulate air pollution and mortality in 20 U.S. cities, 1987-1994." N Engl J Med **343**(24): 1742-1749.

Samet, J. M., S. L. Zeger, F. Dominici, F. Curriero, I. Coursac, D. W. Dockery, J. Schwartz and A. Zanobetti (2000b). "The National Morbidity, Mortality, and Air Pollution Study. Part II: Morbidity and mortality from air pollution in the United States." Res Rep Health Eff Inst **94**(Pt 2): 5-70; discussion 71-79.

Samoli, E., A. Zanobetti, J. Schwartz, R. Atkinson, A. LeTertre, C. Schindler, L. Perez, E. Cadum, J. Pekkanen, A. Paldy, G. Touloumi and K. Katsouyanni (2009). "The temporal pattern of mortality responses to ambient ozone in the APHEA project." J Epidemiol Community Health **63**(12): 960-966.

Schelegle, E. S., C. A. Morales, W. F. Walby, S. Marion and R. P. Allen (2009). "6.6-hour inhalation of ozone concentrations from 60 to 87 parts per billion in healthy humans." Am J Respir Crit Care Med **180**(3): 265-272.

Schiffman, S. S., C. E. Studwell, L. R. Landerman, K. Berman and J. S. Sundy (2005a). "Symptomatic effects of exposure to diluted air sampled from a swine confinement atmosphere on healthy human subjects." Environ Health Perspect **113**(5): 567-576.

Schiffman, S. S. and C. M. Williams (2005b). "Science of odor as a potential health issue." J Environ Qual **34**(1): 129-138.

Schinasi, L., R. A. Horton, V. T. Guidry, S. Wing, S. W. Marshall and K. B. Morland (2011). "Air pollution, lung function, and physical symptoms in communities near concentrated Swine feeding operations." Epidemiology **22**(2): 208-215.

Seaton, A., W. MacNee, K. Donaldson and D. Godden (1995). "Particulate air pollution and acute health effects." Lancet **345**(8943): 176-178.

Shah, A. S., K. K. Lee, D. A. McAllister, A. Hunter, H. Nair, W. Whiteley, J. P. Langrish, D. E. Newby and N. L. Mills (2015). "Short term exposure to air pollution and stroke: systematic review and meta-analysis." Bmj **350**: h1295.

Sherwin, R. P. (1991). "Air pollution: the pathobiologic issues." J Toxicol Clin Toxicol **29**(3): 385-400.

Shin, H. H., N. Fann, R. T. Burnett, A. Cohen and B. J. Hubbell (2014). "Outdoor fine particles and nonfatal strokes: systematic review and meta-analysis." Epidemiology **25**(6): 835-842.

Shusterman, D. (2001). "Odor-associated health complaints: competing explanatory models." Chem Senses **26**(3): 339-343.

Shusterman, D., J. Lipscomb, R. Neutra and K. Satin (1991). "Symptom prevalence and odor-worry interaction near hazardous waste sites." Environ Health Perspect **94**: 25-30.

Sienra-Monge, J. J., M. Ramirez-Aguilar, H. Moreno-Macias, N. I. Reyes-Ruiz, B. E. Del Rio-Navarro, M. X. Ruiz-Navarro, G. Hatch, K. Crissman, R. Slade, R. B. Devlin and I. Romieu (2004). "Antioxidant supplementation and nasal inflammatory responses among young asthmatics exposed to high levels of ozone." Clinical and Experimental Immunology **138**(2): 317-322.

Solic, J. J., M. J. Hazucha and P. A. Bromberg (1982). "The acute effects of 0.2 ppm ozone in patients with chronic obstructive pulmonary disease." American Review of Respiratory Disease **125**(6): 664-669.

Song, S., D. Paek, C. Park, C. Lee, J. H. Lee and S. D. Yu (2013). "Exposure to ambient ultrafine particles and urinary 8-hydroxyl-2-deoxyguanosine in children with and without eczema." Sci Total Environ **458-460**: 408-413.

South Coast Air Quality Management District. (1996). "1996 Air Quality Management Plan, Appendix I: Health Effects." Diamond Bar, CA South Coast Air Quality Management District. from http://www.aqmd.gov/home/library/clean-air-plans/air-quality-mgt-plan/1997-aqmp.

South Coast Air Quality Management District. (2000). "Multiple Air Toxics Exposure Study in the South Coast Air Basin (MATES-II)." Diamond Bar, CA South Coast Air Quality Management District. from http://www.aqmd.gov/home/library/air-quality-data-studies/health-studies/mates-ii.

South Coast Air Quality Management District. (2003). "2003 Air Quality Management Plan, Appendix I: Health Effects." Diamond Bar, CA South Coast Air Quality Management District. from

http://www.aqmd.gov/docs/default-source/clean-air-plans/air-quality-management-plans/2003-air-quality-management-plan/2003-aqmp-appendix-i.pdf?sfvrsn=2.

South Coast Air Quality Management District. (2007). "2007 Air Quality Management Plan, Appendix I: Health Effects." Diamond Bar, CA South Coast Air Quality Management District. from http://www.aqmd.gov/docs/default-source/clean-air-plans/air-quality-management-plans/2007-air-quality-management-plan/2007-aqmp-appendix-i.pdf?sfvrsn=2.

South Coast Air Quality Management District. (2008). "Multiple Air Toxics Exposure Study in the South Coast Air Basin (MATES-III)." Diamond Bar, CA South Coast Air Quality Management District from http://www.aqmd.gov/home/library/air-quality-data-studies/health-studies/mates-iii.

South Coast Air Quality Management District. (2012). "Socioeconomic Report for the 2012 AQMP." Diamond Bar, CA South Coast Air Quality Management District. from http://www.aqmd.gov/docs/default-source/clean-air-plans/air-quality-management-plans/2012-air-quality-management-plan/final-2012-aqmp-(february-2013)/final-socioeconomic-report-2012.pdf?sfvrsn=2.

South Coast Air Quality Management District. (2013a). "2012 Air Quality Management Plan." Diamond Bar, CA South Coast Air Quality Management District.

South Coast Air Quality Management District. (2013b). "2012 Air Quality Management Plan, Appendix I: Health Effects." Diamond Bar, CA South Coast Air Quality Management District. from http://www.aqmd.gov/docs/default-source/clean-air-plans/air-quality-management-plans/2012-air-quality-management-plan/final-2012-aqmp-(february-2013)/appendix-i-final-2012.pdf.

South Coast Air Quality Management District. (2015). "Multiple Air Toxics Exposure Study in the South Coast Air Basin (MATES-IV)." Diamond Bar, CA South Coast Air Quality Management District. from http://www.aqmd.gov/home/library/air-quality-data-studies/health-studies/mates-iv.

Sram, R. J., B. Binkova, J. Dejmek and M. Bobak (2005). "Ambient air pollution and pregnancy outcomes: a review of the literature." Environ Health Perspect **113**(4): 375-382.

Stafoggia, M., F. Forastiere, A. Faustini, A. Biggeri, L. Bisanti, E. Cadum, A. Cernigliaro, S. Mallone, P. Pandolfi, M. Serinelli, R. Tessari, M. A. Vigotti and C. A. Perucci (2010). "Susceptibility factors to ozone-related mortality: a population-based case-crossover analysis." Am J Respir Crit Care Med **182**(3): 376-384.

Stieb, D. M., L. Chen, M. Eshoul and S. Judek (2012). "Ambient air pollution, birth weight and preterm birth: a systematic review and meta-analysis." Environ Res **117**: 100-111.

Stingone, J. A., T. J. Luben, J. L. Daniels, M. Fuentes, D. B. Richardson, A. S. Aylsworth, A. H. Herring, M. Anderka, L. Botto, A. Correa, S. M. Gilboa, P. H. Langlois, B. Mosley, G. M. Shaw, C. Siffel and A. F. Olshan (2014). "Maternal exposure to criteria air pollutants and congenital heart defects in offspring: Results from the national birth defects prevention study." Environmental Health Perspectives **122**(8): 863-872.

Straney, L., J. Finn, M. Dennekamp, A. Bremner, A. Tonkin and I. Jacobs (2014). "Evaluating the impact of air pollution on the incidence of out-of-hospital cardiac arrest in the Perth Metropolitan Region: 2000-2010." Journal of Epidemiology and Community Health **68**(1): 6-12.

Strickland, M. J., L. A. Darrow, M. Klein, W. D. Flanders, J. A. Sarnat, L. A. Waller, S. E. Sarnat, J. A. Mulholland and P. E. Tolbert (2010). "Short-term associations between ambient air pollutants and pediatric asthma emergency department visits." Am J Respir Crit Care Med **182**(3): 307-316.

Sunyer, J., M. Esnaola, M. Alvarez-Pedrerol, J. Forns, I. Rivas, M. Lopez-Vicente, E. Suades-Gonzalez, M. Foraster, R. Garcia-Esteban, X. Basagana, M. Viana, M. Cirach, T. Moreno, A. Alastuey, N. Sebastian-Galles, M. Nieuwenhuijsen and X. Querol (2015). "Association between traffic-related air pollution in schools and cognitive development in primary school children: a prospective cohort study." PLoS Med **12**(3): e1001792.

Symanski, E., M. K. McHugh, X. Zhang, E. S. Craft and D. Lai (2016). "Evaluating narrow windows of maternal exposure to ozone and preterm birth in a large urban area in Southeast Texas." J Expo Sci Environ Epidemiol **26**(2): 167-172.

Thurston, G. D., J. Ahn, K. R. Cromar, Y. Shao, H. R. Reynolds, M. Jerrett, C. C. Lim, R. Shanley, Y. Park and R. B. Hayes (2016). "Ambient Particulate Matter Air Pollution Exposure and Mortality in the NIH-AARP Diet and Health Cohort." Environ Health Perspect **124**(4): 484-490.

Trasande, L., K. Wong, A. Roy, D. A. Savitz and G. Thurston (2013). "Exploring prenatal outdoor air pollution, birth outcomes and neonatal health care utilization in a nationally representative sample." J Expo Sci Environ Epidemiol **23**(3): 315-321.

Turner, M. C., M. Jerrett, C. A. Pope, 3rd, D. Krewski, S. M. Gapstur, W. R. Diver, B. S. Beckerman, J. D. Marshall, J. Su, D. L. Crouse and R. T. Burnett (2016). "Long-Term Ozone Exposure and Mortality in a Large Prospective Study." Am J Respir Crit Care Med **193**(10): 1134-1142.

U.S. EPA. (2000). "Air Quality Criteria for Carbon Monoxide Final Report." Washington, DC U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment.

U.S. EPA. (2004). "Air Quality Criteria for Particulate Matter (Final Report, Oct 2004)." Washington, DC U.S. Environmental Protection Agency. from https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=87903.

U.S. EPA. (2006). "Air Quality Criteria for Ozone and Related Photochemical Oxidants (2006 Final)." Washington, DC U.S. Environmental Protection Agency. from https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=149923.

U.S. EPA. (2007). "Review of the National Ambient Air Quality Standards for Lead: Policy Assessment of Scientific and Technical Information " Washington, DC U.S. Environmental Protection Agency. EPA-452/R-07-013.

U.S. EPA. (2008). "Integrated Science Assessment (ISA) for Sulfur Oxides – Health Criteria (Final Report)." Washington, DC U.S. Environmental Protection Agency. EPA/600/R-08/047F.

U.S. EPA. (2009). "Integrated Science Assessment for Particulate Matter (Final Report)." Washington, DC U.S. Environmental Protection Agency. EPA/600/R-08/139F.

U.S. EPA. (2010). "Integrated Science Assessment for Carbon Monoxide (Final Report)." Washington, DC U.S. Environmental Protection Agency. EPA/600/R-09/019F.

U.S. EPA. (2012). "Regulatory Impact Analysis related to the Proposed Revisions to the National Ambient Air Quality Standards for Particulate Matter " Washington, DC U.S. Environmental Protection Agency. EPA-452/R-12-003.

U.S. EPA. (2013a). "Final Report: Integrated Science Assessment for Lead." Washington, DC U.S. Environmental Protection Agency. EPA/600/R-10/075F.

U.S. EPA. (2013b). "Integrated Science Assessment of Ozone and Related Photochemical Oxidants." Washington, DC U.S. Environmental Protection Agency. EPA/600/R-10/076F.

U.S. EPA (2013c). National Ambient Air Quality Standards for Particulate Matter; Final Rule (January 15, 2013). U. S. EPA. Washington, D.C., Federal Register. **Vol. 78, No. 10:** 3086-3287.

U.S. EPA. (2015a). "Draft Integrated Science Assessment for Sulfur Oxides-Health Criteria." Federal Register Washington, DC U.S. Environmental Protection Agency. 80 FR 73183, from https://federalregister.gov/a/2015-29800.

U.S. EPA. (2015b). "National Ambient Air Quality Standards (NAAQS) for Ozone." Federal Register Washington, DC U.S. Environmental Protection Agency. Vol. 80, No. 206.

U.S. EPA. (2015c). "National Ambient Air Quality Standards for Lead. Proposed Rule." Federal Register Washington, DC U.S. Environmental Protection Agency. Vol, 80, No. 2.

U.S. EPA. (2016). "Integrated Science Assessment for Oxides of Nitrogen – Health Criteria." Washington, DC U.S. Environmental Protection Agency. EPA/600/R-15/068.

Van Bree, L., J. A. M. A. Dormans, H. S. Koren, R. B. Devlin and P. J. A. Rombout (2002). "Attenuation and recovery of pulmonary injury in rats following short-term, repeated daily exposure to ozone." Inhalation Toxicology **14**(8): 883-900.

Vedal, S. (1997). "Ambient particles and health: lines that divide." J Air Waste Manag Assoc **47**(5): 551-581.

Volk, H. E., F. Lurmann, B. Penfold, I. Hertz-Picciotto and R. McConnell (2013). "Traffic-related air pollution, particulate matter, and autism." JAMA Psychiatry **70**(1): 71-77.

Wagner, J. G., K. Allen, H. Y. Yang, B. Nan, M. Morishita, B. Mukherjee, J. T. Dvonch, C. Spino, G. D. Fink, S. Rajagopalan, Q. Sun, R. D. Brook and J. R. Harkema (2014). "Cardiovascular depression in rats exposed to inhaled particulate matter and ozone: effects of diet-induced metabolic syndrome." Environ Health Perspect **122**(1): 27-33.

Wang, L., B. Wei, Y. Li, H. Li, F. Zhang, M. Rosenberg, L. Yang, J. Huang, T. Krafft and W. Wang (2014). "A study of air pollutants influencing life expectancy and longevity from spatial perspective in China." Science of the Total Environment **487**: 57-64.

Wang, X., W. Kindzierski and P. Kaul (2015). "Comparison of transient associations of air pollution and AMI hospitalisation in two cities of Alberta, Canada, using a case-crossover design." BMJ Open **5**(11): e009169.

Wei, Y., J. J. Zhang, Z. Li, A. Gow, K. F. Chung, M. Hu, Z. Sun, L. Zeng, T. Zhu, G. Jia, X. Li, M. Duarte and X. Tang (2016). "Chronic exposure to air pollution particles increases the risk of obesity and metabolic syndrome: findings from a natural experiment in Beijing." Faseb j.

Wendt, J. K., E. Symanski, T. H. Stock, W. Chan and X. L. Du (2014). "Association of short-term increases in ambient air pollution and timing of initial asthma diagnosis among Medicaid-enrolled children in a metropolitan area." Environ Res 131: 50-58.

Wenten, M., W. J. Gauderman, K. Berhane, P. C. Lin, J. Peters and F. D. Gilliland (2009). "Functional variants in the catalase and myeloperoxidase genes, ambient air pollution, and respiratory-related school absences: an example of epistasis in gene-environment interactions." Am J Epidemiol 170(12): 1494-1501.

White, L. F., M. Jerrett, J. Yu, J. D. Marshall, L. Rosenberg and P. F. Coogan (2016). "Ambient Air Pollution and 16-Year Weight Change in African-American Women." Am J Prev Med.

Wilhelm, M., J. K. Ghosh, J. Su, M. Cockburn, M. Jerrett and B. Ritz (2012). "Traffic-related air toxics and term low birth weight in Los Angeles County, California." Environ Health Perspect 120(1): 132-138.

Wilhelm, M. and B. Ritz (2005). "Local variations in CO and particulate air pollution and adverse birth outcomes in Los Angeles County, California, USA." Environ Health Perspect 113(9): 1212-1221.

Wilson, D. A., W. Xu, B. Sadrian, E. Courtiol, Y. Cohen and D. C. Barnes (2014). "Cortical odor processing in health and disease." Prog Brain Res 208: 275-305.

Winquist, A., E. Kirrane, M. Klein, M. Strickland, L. A. Darrow, S. E. Sarnat, K. Gass, J. Mulholland, A. Russell and P. Tolbert (2014). "Joint effects of ambient air pollutants on pediatric asthma emergency department visits in Atlanta, 1998-2004." Epidemiology 25(5): 666-673.

Wittkopp, S., N. Staimer, T. Tjoa, D. Gillen, N. Daher, M. Shafer, J. J. Schauer, C. Sioutas and R. J. Delfino (2013). "Mitochondrial genetic background modifies the relationship between traffic-related air pollution exposure and systemic biomarkers of inflammation." PLoS ONE 8(5): e64444.

Wong, C. M., N. Vichit-Vadakan, N. Vajanapoom, B. Ostro, T. Q. Thach, P. Y. Chau, E. K. Chan, R. Y. Chung, C. Q. Ou, L. Yang, J. S. Peiris, G. N. Thomas, T. H. Lam, T. W. Wong, A. J. Hedley, H. Kan, B. Chen, N. Zhao, S. J. London, G. Song, G. Chen, Y. Zhang, L. Jiang, Z. Qian, Q. He, H. M. Lin, L. Kong, D. Zhou, S. Liang, Z. Zhu, D. Liao, W. Liu, C. M. Bentley, J. Dan, B. Wang, N. Yang, S. Xu, J. Gong, H. Wei, H. Sun and Z. Qin (2010). "Part 5. Public health and air pollution in Asia (PAPA): a combined analysis of four studies of air pollution and mortality." Res Rep Health Eff Inst(154): 377-418.

Yang, W. S., X. Wang, Q. Deng, W. Y. Fan and W. Y. Wang (2014). "An evidence-based appraisal of global association between air pollution and risk of stroke." International Journal of Cardiology 175(2): 307-313.

Yorifuji, T., S. Kashima and H. Doi (2015). "Outdoor air pollution and term low birth weight in Japan." Environment International 74: 106-111.

Young, M. T., D. P. Sandler, L. A. DeRoo, S. Vedal, J. D. Kaufman and S. J. London (2014). "Ambient air pollution exposure and incident adult asthma in a nationwide cohort of U.S. women." Am J Respir Crit Care Med 190(8): 914-921.

Zanobetti, A. and J. Schwartz (2008). "Mortality displacement in the association of ozone with mortality: an analysis of 48 cities in the United States." <u>Am J Respir Crit Care Med</u> **177**(2): 184-189.

Zanobetti, A. and J. Schwartz (2009). "The effect of fine and coarse particulate air pollution on mortality: a national analysis." <u>Environ Health Perspect</u> **117**(6): 898-903.

Zanobetti, A. and J. Schwartz (2011). "Ozone and survival in four cohorts with potentially predisposing diseases." <u>Am J Respir Crit Care Med</u> **184**(7): 836-841.

Zeger, S. L., F. Dominici, A. McDermott and J. M. Samet (2008). "Mortality in the Medicare population and chronic exposure to fine particulate air pollution in urban centers (2000-2005)." <u>Environ Health Perspect</u> **116**(12): 1614-1619.

Zhu, Y., W. C. Hinds, S. Kim and C. Sioutas (2002). "Concentration and size distribution of ultrafine particles near a major highway." <u>J Air Waste Manag Assoc</u> **52**(9): 1032-1042.

Zu, K., G. Tao, C. Long, J. Goodman and P. Valberg (2016). "Long-range fine particulate matter from the 2002 Quebec forest fires and daily mortality in Greater Boston and New York City." <u>Air Qual Atmos Health</u> **9**: 213-221.

DRAFT FINAL 2016 AQMP
APPENDIX I
Attachment

**Publications from Health Related Research Projects
Funded or Co-Funded by SCAQMD**

DECEMBER 2016

PREFACE TO THE ATTACHMENT

This attachment provides a list of health-related publications from studies that were funded or partially funded by the SCAQMD. These include several studies that focus on evaluating health outcomes in Southern California populations, or toxicological effects of pollutants within the Southern California region. While an assessment of causality and strength of evidence should include air pollution studies conducted in many places, including other parts of the U.S. and in other countries, health studies focusing on Southern California provide an important "local perspective" in understanding and evaluating ~~the discussion of~~ the health effects of air pollution. Some of these studies funded by SCAQMD were discussed in Appendix I, as appropriate, although the Appendix I also included many other studies that are not on this list. These studies funded by SCAQMD also help inform the SCQAMD's work in characterizing the air pollution in our local region and the influences of sources of air pollution in the Basin.

A new compact aerosol concentrator for use in conjunction with low flow-rate continuous aerosol instrumentation
Michael D. Geller∗, Subhasis Biswas, Philip M. Fine, Constantinos Sioutas
Aerosol Science 36 1006–1022, 2005

Air Pollution and Type 2 Diabetes Prevalence, Control, and Risk Factors. Final Report.
Ying-Ying Meng, Susan Babey, Michael Jerrett
UCLA Center for Health Policy Research, 2014

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 submitted to BP SCAQMD Public Benefits Oversight Committee, October 22, 2014

Air pollution exposures and circulating biomarkers of effect in a susceptible population: clues to potential causal component mixtures and mechanisms.
Delfino RJ, Staimer N, Tjoa T, Gillen DL, Polidori A, Arhami M, Kleinman MT, Vaziri ND, Longhurst J, Sioutas C.
Environ Health Perspect.117(8):1232-8, 2009

Airway inflammation and oxidative potential of air pollutant particles in a pediatric asthma panel
Ralph J. Delfino, Norbert Staimer, Thomas Tjoa, Daniel L. Gillen James J. Schauer, and Martin M. Shafer
J Expo Sci Environ Epidemiol.; 23(5): 466–473, 2013

Ambient air pollution and brain cancer mortality
Roberta McKean-Cowdin, Eugenia E. Calle, John M. Peters, Jane Henley, Lindsay Hannan, George D. Thurston, Michael J. Thun, Susan Preston-Martin
Cancer Causes Control 20:1645–1651, 2009

Ambient ozone concentrations and cardiac mortality in Southern California 1983-2000: application of a new marginal structural model approach.
Moore K, Neugebauer R, Lurmann F, Hall J, Brajer V, Alcorn S, Tager I.
Am J Epidemiol. 2010 Jun 1;171(11):1233-43.

Ambient ozone concentrations cause increased hospitalizations for asthma in children: an 18-year study in Southern California.
Moore K, Neugebauer R, Lurmann F, Hall J, Brajer V, Alcorn S, Tager I.
Environ Health Perspect. 2008 Aug;116(8):1063-70.

Ambient Vapor Samples Activate the Nrf2-ARE Pathway in Human Bronchial Epithelial BEAS-2B Cells
Yasuhiro Shinkai, Syun Nakajima, Arantza Eiguren-Fernandez, Emma Di Stefano, Debra A. Schmitz, John R. Froines, Arthur K. Cho, Yoshito Kumagai
Environ Toxicol. (11):1292-300, 2014

Associations Between Particle Number and Gaseous Co-Pollutant Concentrations in the Los Angeles Basin.
Sardar S.B., Fine P.M., Yoon H. and Sioutas C.
Journal of the Air and Waste Management Association. 5: 4992-1005, 2004

Associations of Primary and Secondary Organic Aerosols With Airway and Systemic Inflammation in an Elderly Panel Cohort
Ralph J. Delfino, Norbert Staimer, Thomas Tjoa, Mohammad Arhami, Andrea Polidori, Daniel L. Gillen, Steven C. George, Martin M. Shafer, James J. Schauer, Constantinos Sioutas
Epidemiology 21: 892–902, 2010

Asthma Morbidity and Ambient Air Pollution. Effect Modification by Residential Traffic-Related Air Pollution
Ralph J. Delfino, Jun Wu, Thomas Tjoa, Sevan K. Gullesserian, Bruce Nickerson, Daniel L. Gillen
Epidemiology 25(1): 48-57, 2014

Bioassay Analyses of Emissions from Compressed Natural Gas and Ultra-Low Sulfur Diesel Fueled Transit Buses (Final Report).
Kado, N. Y., & Kuzmicky, P. A.
Report to The South Coast Air Quality Management District., 2003

Characterization of particle bound organic carbon from diesel vehicles equipped with advanced emission control technologies.
Pakbin, P.; Ning, Z.; Schauer, J. J.; Sioutas, C.,
Environ Sci Technol 43(13) : 4679-4686, 2009

Characterization of particulate matter and co-pollutants during the fall 2003 Southern California fires.
Phuleria, H., Fine, P. M., Zhu, Y., & Sioutas, C.
Journal of Geophysical Research, 110, D07S20 (2005).

Characterizing the range of children's air pollutant exposure during school bus commutes
Lisa D. Sabin, Eduardo Behrentz, Arthur M. Winer, Seong Jeong, Dennis R. Fitz, David V. Pankratz, Steven D. Colome, Scott A. Fruin
Journal of Exposure Analysis and Environmental Epidemiology 15: 377–387, 2005

Chemical reactivities of ambient air samples in three Southern California communities
Arantza Eiguren-Fernandez, Emma Di Stefano, Debra A. Schmitz, Aline Lefol Nani Guarieiro, Erika M. Salinas, Elina Nasser, John R. Froines, Arthur K. Cho
Journal of the Air & Waste Management Association, 65:3, 270-277, 2015

Chemical Speciation of Exhaust Emissions from Trucks and Buses Fueled on Ultra-Low Sulfur Diesel and CNG, Miriam Lev-On, Chuck LeTavec, Jim Uihlein, Teresa L. Alleman, Douglas R. Lawson, Keith Vertin, Gregory J. Thompson, Mridul Gautam, Scott Wayne, Barbara Zielinska, John Sagebiel,
SAE Technical Paper Series 2002-01-0432, 2002

Childhood Brain Tumors and Air Pollution: The West Coast Childhood Brain Tumor Study, Final Report. Roberta McKean-Cowdin, Michael Jerrett, Susan Preston-Martin. The University of Southern California (USC), Los Angeles, November 2011

Childhood Incident Asthma and Traffic-Related Air Pollution at Home and School
Rob McConnell, Talat Islam, Ketan Shankardass, Michael Jerrett, Fred Lurmann, Frank Gilliland, Jim Gauderman, Ed Avol, Nino Künzli, Ling Yao, John Peters, and Kiros Berhane
Environ Health Perspect 118:1021–1026 (2010)

Circulating biomarkers of inflammation, antioxidant activity, and platelet activation are associated with primary combustion aerosols in subjects with coronary artery disease.
Delfino RJ, Staimer N, Tjoa T, Polidori A, Arhami M, Gillen DL, Kleinman MT, Vaziri ND, Longhurst J, Zaldivar F, Sioutas C.
Environ Health Perspect.116(7):898-906, 2008

Coarse Particles and Daily Mortality in Coachella Valley, California
Bart D Ostro, Rachel Broadwin, and Michael J Lipsett
In: Health Effects Institute. Revised Analyses of Time-Series Studies of Air Pollution and Health. Special Report. Health Effects Institute, Boston MA. 2003.

Combustion Exhaust and the Respiratory Health of Port Community Children. Ed Avol, Jim Gauderman, Robert Urman, Department of Preventive Medicine, Keck School of Medicine of USC, Fred Lurmann, Sonoma Technology, Incorporated, 2009
Final Report to the South Coast Air Quality Management District Contract #07359 (Nov 2009),

Cost of near-roadway and regional air pollution–attributable childhood asthma in Los Angeles County
Sylvia Brandt, Laura Perez, Nino Kunzli, Fred Lurmann, John Wilson, Manuel Pastor, Rob McConnell
J Allergy Clin Immunol 134(5): 1028-1035

Costs of childhood asthma due to traffic-related pollution in two California communities
S.J. Brandt, L. Perez N. Künzli, F. Lurmann, R. McConnell
Eur Respir J. 40(2):363-70, 2012;

Effect of advanced aftertreatment for PM and NOx reduction on heavy-duty diesel engine ultrafine particle emissions.
Herner JD, Hu S, Robertson WH, Huai T, Chang MC, Rieger P, Ayala A.
Environ Sci Technol.45(6):2413-9, 2011.

Electrocardiographic ST-segment depression and exposure to traffic-related aerosols in elderly subjects with coronary artery disease.
Delfino RJ, Gillen DL, Tjoa T, Staimer N, Polidori A, Arhami M, Sioutas C, Longhurst J.
Environ Health Perspect. Feb;119(2):196-202, 2011

Experiences of a rail yard community: life is hard.
Spencer-Hwang R, Montgomery S, Dougherty M, Valladares J, Rangel S, Gleason P, Soret S.
J Environ Health 77(2):8-17, 2014

Field Validation of the New Miniature Versatile Aerosol Concentration Enrichment System (mVACES)
Zhi Ning, Katharine F. Moore, Andrea Polidori, and Constantinos Sioutas
Aerosol Science and Technology, 40:1098–1110, 2006

Gene expression changes in rat brain after short and long exposures to particulate matter in Los Angeles basin air: Comparison with human brain tumors
Julia Y. Ljubimova, Michael T. Kleinman, Natalya M. Karabalin, Satoshi Inoue, Bindu Konda, Pallavi Gangalum, Janet L. Markman, Alexander V. Ljubimov, Keith L. Black
Experimental and Toxicologic Pathology 65 (2013) 1063– 1071

Global perspective on the oxidative potential of airborne particulate matter: a synthesis of research findings. A. Saffari, N. Daher, M. M. Shafer, J.J. Schauer, C. Sioutas. Environmental Science and Technology, 2014, 48, 7576-7583.

Health Effects of the 2003 Southern California Wildfires on Children
Nino Kunzli, Ed Avol, Jun Wu, W. James Gauderman, Ed Rappaport, Joshua Millstein, Jonathan Bennion, Rob McConnell, Frank D. Gilliland, Kiros Berhane, Fred Lurmann, Arthur Winer, and John M. Peters
Am J Respir Crit Care Med Vol 174. pp 1221–1228, 2006

Human brain derived cells respond in a type-specific manner after exposure to urban particulate matter (PM)
Arezoo Campbell, Nancy Daher, Parrisa Solaimani, Kriscelle Mendoza, Constantinos Sioutas
Toxicology in Vitro 28(7): 1290–1295, 2014

Macrophage Reactive Oxygen Species Activity of Water-soluble and Water-insoluble Fractions of Ambient Coarse, PM2.5 and Ultrafine Particulate Matter (PM) in Los Angeles.
D. Wang, P. Pakbin, M. M. Shafer, D. Antkiewicz, J. J. Schauer and C. Sioutas.
Atmospheric Environment, 77, 301-310, 2013.

Making Human Subject Protection Training Community Responsive: Experiences Delivering on the Community-Based Participatory Research Promise
Rhonda Spencer-Hwang, Sam Soret, Linda Halstead, Molly Dougherty, Johanny Valladares, Sany Rangel, Caroline Youssef, Thelma Maldonado-Gamboa, Susanne Montgomery.
Progress in Community Health Partnerships: Research, Education, and Action 8(2): 215-224, 2014

Metals emitted from heavy-duty diesel vehicles equipped with advanced PM
and NOX emission controls
Shaohua Hu, Jorn D. Herner, Martin Shafeb, William Robertson, James J. Schauer, Harry Dwyer, John Collins, Tao Huai, Alberto Ayala
Atmospheric Environment 43: 2950–2959, 2009

Molecular Changes in Rat Brain Due to Air Nano Pollution.
Ljubimova JY, Gangalum PR, Portilla-Arias J, Patil R, Konda B, Paff M, Markman J, Inoue S, Espinoza A, Chesnokova A, Kleinman M, Holler E, Black KL.
NSTI-Nanotech, www.nsti.org, ISBN 978-1-4665-6276-9, vol.3: 261-263, 2012

Near-Roadway Air Pollution and Coronary Heart Disease: Burden of Disease and Potential Impact of a Greenhouse Gas Reduction Strategy in Southern California
Rakesh Ghosh, Frederick Lurmann, Laura Perez, Bryan Penfold, Sylvia Brandt, John Wilson, Meredith Milet, Nino Künzli, Rob McConnell
Environ Health Perspect. Advance Publication: 7 July 2015

Near-Roadway Pollution and Childhood Asthma: Implications for Developing "Win–Win" Compact Urban Development and Clean Vehicle Strategies
Laura Perez, Fred Lurmann, John Wilson, Manuel Pastor, Sylvia J. Brandt, Nino Künzli, Rob McConnell
Environ Health Perspect 120:1619–1626, 2012

On the interaction between glyceraldehyde-3-phosphate dehydrogenase and airborne particles: Evidence for electrophilic species
Masaru Shinyashiki, Chester E. Rodriguez, Emma W. Di Stefano, Constantinos Sioutas, Ralph J. Delfino, Yoshito Kumagai, John R. Froines, Arthur K. Cho
Atmospheric Environment 42(3): 517–529, 2008

Oxidative Potential of Semi-Volatile and Non Volatile Particulate Matter (PM) from Heavy-Duty Vehicles Retrofitted with Emission Control Technologies
Subhasis Biswas, Vishal Verma, James J. Schauer, Flemming R. Cassee, Arthur K. Cho, Constantinos Sioutas
Environ. Sci. Technol., 43(10): 3905–3912, 2009

Physical properties of particulate matter (PM) from late model heavy-duty diesel vehicles operating with advanced PM and NOx emission control technologies
Subhasis Biswas, Shaohua Hu, Vishal Verma, Jorn D. Herner, William H. Robertson, Alberto Ayala, Constantinos Sioutas.
Atmospheric Environment. 42(22): 5622–5634, 2008

Primary Particulate Matter from Ocean-Going Engines in the Southern California Air Basin
Harshit Agrawal, Rudy Eden, Xinqiu Zhang, Philip M. Fine, Aaron Katzenstein, J. Wayne Miller, Jean Ospital, Solomon Teffera and David R. Cocker, III
Environ. Sci. Technol., 2009, 43 (14), pp 5398–5402

Real-time characterization of particle-bound polycyclic aromatic hydrocarbons in ambient aerosols and from motor-vehicle exhaust.
Polidori, A.; Hu, S.; Biswas, S.; Delfino, R. J.; Sioutas, C.,
Atmos. Chem. Phys. 8: 1277-1291, 2008

Redox and Electrophilic Properties of Vapor- and Particle-Phase Components of Ambient Aerosols
Arantzazu Eiguren-Fernandez, Masaru Shinyashiki, Debra A. Schmitz, Emma DiStefano, William Hinds, Yoshito Kumagai, Arthur K. Cho, John R. Froines
Environ Res. 110(3): 207–212, 2010

Relative Importance of School Bus-Related Microenvironments to Children's Pollutant Exposure.
Eduardo Behrentz, Lisa D. Sabin, Arthur M. Winer, Dennis R. Fitz, David V. Pankratz, Steven D. Colome, Scott A. Fruin.
Journal of the Air & Waste Management Association, 55(10): 1418-1430, 2005

Repeated hospital encounters for asthma in children and exposure to traffic-related air pollution near the home.
Ralph J. Delfino,; Joyce Chang, Jun Wu, ; Cizao Ren, Thomas Tjoa, Bruce Nickerson, Dan Cooper, Daniel L. Gillen,
Ann Allergy Asthma Immunol. 2009;102:138–144

Respiratory Health Risks for Children Living Near a Major Railyard
Rhonda Spencer-Hwang, Sam Soret, Synnove Knutsen, David Shavlik, Mark Ghamsary, W. Lawrence Beeson, Wonha Kim, Susanne Montgomery
J Community Health. 2015 Apr 19. [Epub ahead of print]

Respiratory symptoms and peak expiratory flow in children with asthma in relation to volatile organic compounds in exhaled breath and ambient air.
Delfino RJ, Gong H, Linn WS, Hu Y, Pellizzari ED.
J Expo Anal Environ Epidemiol. 2003 Sep;13(5):348-63.

Source apportionment and organic compound characterization of ambient ultrafine particulate matter (PM) in the Los Angeles Basin.
S. Hasheminassab, N. Daher, J.J. Schauer, C. Sioutas.
Atmospheric Environment, 79, 529-539, 2013.

Seasonal and spatial trends in particle number concentrations and size distributions at the children's health study sites in Southern California.
Singh M, Phuleria HC, Bowers K, Sioutas C.
J Expo Sci Environ Epidemiol. 2006 Jan;16(1):3-18.

Seasonal and spatial variability in chemical composition and mass closure of ambient ultrafine particles in the megacity of Los Angeles.
N. Daher, S. Hasheminassab, M.M. Shafer, J.J. Schauer, C. Sioutas.
Environmental Science: Processes and Impacts, 15, 283-295, 2013.

Seasonal and spatial variation in dithiothreitol (DTT) activity of quasi-ultrafine particles in the Los Angeles Basin and its association with chemical species.
A. Saffari, N. Daher, M. M. Shafer, J.J. Schauer, C. Sioutas.
Journal of Environmental Science and Health, Part A: Toxic/Hazardous Substances and Environmental Engineering, 49 (4), 441-451, 2014

Seasonal and spatial variation in reactive oxygen species activity of quasi-ultrafine particles (PM0.25) in the Los Angeles metropolitan area and its association with chemical composition.
A. Saffari, N. Daher, M. M. Shafer, J.J. Schauer, C. Sioutas..
Atmospheric Environment, 79, 566-575, 2013.

Seasonal and spatial variation of trace elements and metals in quasi-ultrafine (PM0.25) particles in the Los Angeles metropolitan area and characterization of their sources.
A. Saffari., N. Daher, M. M. Shafer, J.J. Schauer, C. Sioutas.
 Environmental Pollution, 181, 14-23, 2013.

Speciation of Organic Compounds from the Exhaust of Trucks and Buses: Effect of Fuel and After-Treatment on Vehicle Emission Profiles,
Lev-On, M., LeTavec, C., Uihlein, J., Kimura, K. et al.
SAE Technical Paper 2002-01-2873, 2002,

The relationship of respiratory and cardiovascular hospital admissions to the southern California wildfires of 2003
L Zhang, T Tjoa and D L Gillen R J Delfino, S Brummel, J Wu, H Stern, B Ostro, M Lipsett, A Winer, D H Street,
Occup. Environ. Med. 2009;66;189-197

Traffic, Susceptibility, and Childhood Asthma
Rob McConnell, Kiros Berhane, Ling Yao, Michael Jerrett, Fred Lurmann, Frank Gilliland, Nino Künzli, Jim Gauderman, Ed Avol, Duncan Thomas, John Peters
Environ Health Perspect 114:766–772, 2006

Ultra Fine Particles from Diesel Engines Induce Vascular Oxidative Stress via JNK Activation
Rongsong Li, Zhi Ning, Jeffery Cui, Bhavraj Khalsa, Lisong Ai, Wakako Takabe, Tyler Beebe, Rohit Majumdar, Constantinos Sioutas,* and Tzung Hsiai
Free Radic Biol Med. 2009 Mar 15; 46(6): 775–782.