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APPENDIX I
VERSION 2

HEALTH EFFECTS

~~SEPTEMBER~~ OCTOBER 2012

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Table of Contents

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 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 revisions. This document, which was prepared to satisfy that requirement, also includes the effects of the other major pollutants.

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:

- ~~Increased~~ 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 ~~chemical~~ 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 weights

The evidence linking these effects to air pollutants is derived from population-based observational and field studies (epidemiological) as well as controlled laboratory studies involving human subjects and animals. There have been an increasing number of studies focusing on the mechanisms (that is, on learning how specific organs, cell types, and ~~biochemicals~~ 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 ~~mostly~~ 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 usually 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, ~~may sometimes~~oftentimes ~~act~~ occur together ~~to harm health more than they would acting separately~~. ~~Nevertheless,~~Evidence for more than additive effects have not been strong and, as a practical matter, health scientists, as well as regulatory officials, usually must deal with one pollutant at a time in adopting air quality standards. To meet the air quality standards, comprehensive plans are developed such as the Air Quality Management Plan (AQMP), and to minimize toxic exposure 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 document.

This summary is drawn substantially from reviews presented previously (SCAQMD, 1996, 2003, 2007), and from reviews on the effects of air pollution by the American Thoracic Society (ATS, 1996), the U.S. EPA reviews for ozone (U.S. EPA, 2006), Carbon Monoxide (U.S. EPA, 2010), and Particulate Matter (U.S. EPA, 2004, 2009), from a published review of the health effects of air pollution (Brunekreef and Holgate, 2002), and from reviews prepared by the California Air Resources Board

and the California EPA Office of the Environmental Health Hazard Assessment for Particulate Matter (CARB~~Cal EPA~~, 2002), ~~and~~ for Ozone (CARB~~Cal EPA~~, 2005) and for NO2 (CARB 2007). Additional materials are from EPA's current and ongoing review of the ozone standard and health effects (EPA, 2011). More detailed citations and discussions on air pollution health effects can be found in these references.[1]

OZONE

Ozone is a highly reactive compound, and is 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, it can penetrate into the gas exchange region of the deep lung.

The EPA primary standard for ozone, adopted in 2008, is 0.075 ppm averaged over eight hours. The California Air Resources Board (CARB) has established standards of 0.09 ppm averaged over one hour and at 0.070 ppm averaged over eight hours.

A number of population groups are potentially at increased risk for ozone exposure effects. In the ongoing review of ozone, the EPA has identified populations as having adequate evidence for increased risk from ozone exposures include individuals with asthma, younger and older age groups, individuals with reduced intake of certain nutrients such as Vitamins C and E, and outdoor workers. There is suggestive evidence for other potential factors, such as variations in genes related to oxidative metabolism or inflammation, gender, socioeconomic status, and obesity. However further evidence is needed.

~~The major subgroups of the population considered to be at increased risk from ozone exposure are outdoor exercising individuals, including children, and people with preexisting respiratory disease(s) such as asthma. The data base identifying the former group as being at increased risk to ozone exposure is much stronger and more quantitative than that for the latter group, probably because of a larger number of studies conducted with healthy individuals.~~ The adverse effects reported with short-term ozone exposure are greater with increased activity because activity increases the breathing rate and the volume of air reaching the lungs, resulting in an increased amount of ozone reaching the lungs. Children may be a particularly vulnerable

[1] Most of the studies referred to in this appendix are cited in the above sources. Only more recent specific references will be cited in this summary.

population to air pollution effects because they spend more time outdoors, are generally more active, and have a higher specific ventilation rate than adults (i.e. after normalization for body mass.

A number of adverse health effects associated with ambient ozone levels have been identified from laboratory and epidemiological studies (EPA, 1996; 2006, 2011; ATS, 1996). These include increased respiratory symptoms, damage to cells of the respiratory tract, decrease in lung function, increased susceptibility to respiratory infection, and increased risk of hospitalization, and increased risk of mortality.

Increases in ozone levels are associated with ~~elevated~~ increased numbers of absences from school. The Children's Health Study, conducted by researchers at the University of Southern California, followed a cohort of children that live in 12 communities in Southern California with differing levels of air pollution for several years. A publication from this study reported that school absences in fourth graders for respiratory illnesses were positively associated with ambient ozone levels. An increase of 20 ppb ozone was associated with an 83% increase in illness-related absence rates (Gilliland, 2001).

The number of hospital admissions and emergency room visits for all respiratory causes (infections, respiratory failure, chronic bronchitis, etc.) including asthma shows a consistent increase as ambient ozone levels increase in a community. These excess hospital admissions and emergency room visits are observed when hourly ozone concentrations are as low as 0.06 to 0.10 ppm.

Numerous recent studies have found positive associations between increases in ozone levels and excess risk of mortality. These associations are strongest during warmer months but overall persist even when other variables including season and levels of particulate matter are accounted for. This indicates that ozone mortality effects may be independent of other pollutants (Bell, 2004).

Multicity studies of short-term ozone exposures (days) and mortality have also examined regional differences. Evidence was provided that there were generally higher ozone-mortality risk estimates in northeastern U.S. cities, with the southwest and urban mid-west cities showing lower or no associations (Smith, 2009; Bell, 2008). Another long-term study of a national cohort found that long-term exposures to ozone were associated with respiratory-related causes of mortality, but not cardiovascular-related causes, when PM2.5 exposure were also included in the analysis.

In the ongoing EPA review, it was concluded that there is adequate evidence for asthmatics to be a potentially at risk population (EPA, 2012c). Several population-based studies suggest that asthmatics are ~~more adversely affected~~at risk from ~~by~~ ambient ozone levels, as evidenced by changes in lung function, increased hospitalizations and emergency room visits.

Laboratory studies ~~have attempted to compare~~have also compared the degree of lung function change seen in age and gender-matched healthy individuals versus asthmatics and those with chronic obstructive pulmonary disease. ~~While~~ In studies of individuals with chronic obstructive pulmonary decease, the degree of change evidenced did not differ significantly. ~~, t~~That finding, however~~, may~~, 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 ~~degree of~~total change may represent a substantially greater relative adverse effect overall. Other studies have found that subjects with asthma ~~are more~~are more sensitive to the short term effects of ozone in terms of lung function and inflammatory response.

Another publication from the Children's Health Study focused on children and outdoor exercise. In southern ~~Caliornia~~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, 2002). These findings indicate that new cases of asthma in children ~~are~~ 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 be causally linked to asthma onset.

In addition, human and animal studies involving both short-term (few hours) and long-term (months to years) exposures indicate a wide range of effects induced or associated with ambient ozone exposure. These are summarized in Table I-1.

TABLE I-1

Adverse Health Effects of Ozone (O3) - Summary of Key ~~Studies~~Findings

0_3 CONCENTRATION AND EXPOSURE HR., PPM	**HEALTH EFFECT**

Ambient air containing 0.10 - 0.15 daily 1-h max over days to weeks; ≥ 0.05 (8 hour average)	Decreased breathing capacity, in children, adolescents, and adults exposed to 0_3 outdoors Exacerbation of respiratory symptoms (e.g., cough, chest pain) in individuals with preexisting disease (e.g., asthma) with low ambient exposure, decreased temperature, and other environmental factors resulting in increased summertime hospital admissions and emergency department visits for respiratory causes with ambient exposures.
≥0.12 (1-3h) ≥0.06 (6.6h) (chamber exposures)	Decrements in lung function (reduced ability to take a deep breath), increased respiratory symptoms (cough, shortness of breath, pain upon deep inspiration), increased airway responsiveness and increased airway inflammation in exercising adults Effects are similar in individuals with preexisting disease except for a greater increase in airway responsiveness for asthmatic and allergic subjects Older subjects (>50 yrs old) have smaller and less reproducible changes in lung function Attenuation of response with repeated exposure
≥0.12 with prolonged, repeated exposure (chamber exposures)	Changes in lung structure, function, elasticity, and biochemistry in laboratory animals that are indicative of airway irritation and inflammation with possible development of chronic lung disease Increased susceptibility to bacterial respiratory infections in laboratory animals

From: SCAQMD, 1996; EPA, 2007, EPA, 2012, Kim 2011

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

In a laboratory, exposure of human subjects to low levels of ozone causes reversible decrease 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. Similar lung volume changes have also been observed in adults and children under ambient exposure conditions (0.10 - 0.15 ppm 1-hour ~~averge~~average). The responses reported are indicative of decreased breathing capacity and are reversible.

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 recently summarized (Brown, 2008). As shown in the figure below, there is an increasing response on lung function with increasing exposure levels in moderately exercising subjects. A more recent study (Kim, 2010) exposed young healthy adults to 0.06 ppm ozone for 6.6 hours ~~wile~~while engaging in intermittent moderate ~~excersise~~exercise. The subjects exhibited a reduction in lung function (FEV1) after exposure.

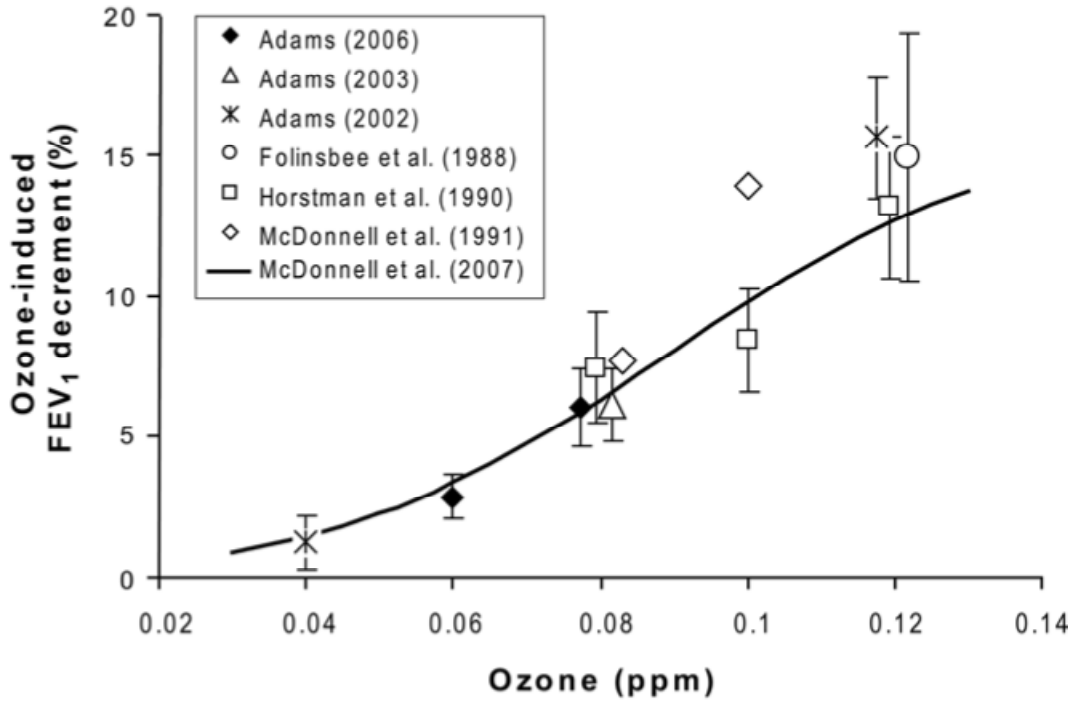


FIGURE I-1
Comparison of mean ozone-induced decrements in lung function following 6.6 hours of ozone exposure (from Brown, 2008)

In addition to controlled laboratory conditions, studies of individuals exercising outdoors, including children attending summer camp, have shown associations of reduced lung function with ozone exposure. There were wide ranges in responses among individuals. EPA's recent review indicates reductions of <1 to 4% in lung function when standardized to an increase of 0.03 ppm for an 8-hour maximum (EPA 2012).

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 (EPA, 2011).

In laboratory studies, cellular and biochemical changes associated with respiratory tract inflammation have also been consistently ~~reported~~ 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 ~~cytokines~~ Interleukin-1, Tumor Necrosis Factor α, and fibronectin. 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~~for up to 6.6 hours with intermittent moderate exercise.

There may be interactions between ozone and other ambient pollutants. The susceptibility to ozone observed under ambient conditions could be modified due to the combination of pollutants that coexist in the atmosphere or ozone ~~may actually~~might sensitize these subgroups to the effects of other pollutants.

Some animal studies show results that indicate possible chronic effects including functional and structural changes of the lung. These changes indicate that repeated inflammation associated with ozone exposure over a lifetime may result in ~~sufficient~~ 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. An autopsy study involving Los Angeles County residents, although conducted many years ago when pollutant levels were higher than currently measured, provided supportive evidence of lung tissue damage (structural changes) attributable to air pollution.

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 ~~is~~ 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. ~~Confirmation by further studies is needed.~~

In summary, adverse effects associated with ozone exposures have been well documented.~~,~~ ~~a~~Although the specific ~~causal~~ mechanisms of actions are not fully identified, there is a strong likihood that oxidation of key enzymes and ~~proterins~~proteins and inflammatory responses play important roles. ~~is still somewhat unclear.~~

It may be instructive to provide the overall EPA staff preliminary conclusions on the causality on ozone health effects for the health outcomes evaluated (EPA, 2011). These are provided in the two tables below. On the basis of the most recent evaluations of ~~oxone~~ozone health effects, EPA's Clean Air Scientific Advisory Committee has recommended that the NAAQS for ozone be reduced and recommended a range in which 0.070 ppm would be the upper limit. This would be consistent with the California air quality standard.

TABLE I-2

Summary of Causal Determinations for Short-Term Exposures to Ozone

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

From EPA, 2011

TABLE I-3

Summary of Causal Determinations for Long-Term Exposures to Ozone

HEALTH CATEGORY	CAUSAL DETERMINATION

Respiratory Effects	Likely to be a causal relationship
Cardiovascular Effects	Suggestive of a causal relationship
Reproductive and Developmental Effects	Suggestive of a causal relationship
Central Nervous System Effects	Suggestive of a causal relationship
Carcinogenicity and Genotoxicity	Inadequate to infer a causal relationship
Mortality	Suggestive of a causal relationship

From EPA, 2011

PARTICULATE MATTER

Airborne particulates are a complex group of pollutants that vary in source, size and composition, depending on location and time. 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, may also be present.

The National Ambient Air Quality Standard for particulate matter was established in 1971, and set limits on the ambient level of Total Suspended Particulates (TSP). In 1987, the national particulate matter standards were revised to cover particles

~~Until several years ago, the health effects of particulates were focused on those~~ sized 10 µm (micrometers) aerodynamic diameter and smaller. These can be inhaled through the upper airways and deposited in the lower airways and gas exchange tissues in the lung. These particles are referred to as PM10. 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. EPA has since rescinded the annual PM10 standard, but kept the 24-hour standard.

In more recent years additional focus has been placed on particles having an aerodynamic diameter of 2.5 µm or less (PM2.5). A greater faction of particles in this size range can penetrate and deposit deep in the lungs. The EPA established standards for PM2.5 in ~~1997,~~1997 and in 2006 ~~recently~~ 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 EPA

promulgated the initial PM2.5 standards in 1997. The California Air Resources Board adopted an air quality standard for PM2.5 in 2002 at 12 µg/m^3 annual average.

Since that time, numerous studies have been published, and some of the key studies were closely scrutinized and ~~analyses repeated~~the data reanalyzed by additional investigators. The reanalyses ~~confirmed the~~confirmed the findings of significant result, and ~~is that~~ there are now substantial new data confirming and extending the range of the adverse health effects of PM2.5 exposures.

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 larger than 2.5 µm (often referred to as the coarse fraction) 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.

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 few years. These are generally referred to as "ultrafine" particles, with diameters of 0.1 µm or less. These particles are mainly from fresh emissions of combustion sources, but are also formed in the atmosphere by condensation of vapors that are emitted or by ~~from~~ chemical or photochemical reactions with other contaminants in the air.

Ultrafine particles have relatively short half lives (minutes to hours) and rapidly grow through condensation and coagulation process into larger particles within the PM2.5 size range. These particles are garnering interest since a limited number of epidemiological and ~~several~~some laboratory studies, though not all~~, indicate~~, indicate that their toxicity may be higher on a mass basis than larger particles. ~~, and t~~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.

There have been several reviews of the health effects of ambient particulate matter (ATS, 1996; Brunekreef, 2002; U.S. EPA, 2004; U.S. EPA, 2009). 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 (Cal EPA, 2002).

The major types of effects associated with particulate matter include:

- Increased mortality
- Exacerbation of respiratory disease and of cardiovascular disease as evidenced by increases in:
  - Respiratory symptoms
  - Cardiovascular symptoms, non-fatal myocardial infarction
  - Hospital admissions and emergency room visits
  - Physician office visits
  - School absences
  - Adverse birth outcomes
  - ~~Work loss days~~
- Effects on lung function
- Changes in lung morphology

The California Air Resources Board has also set air quality standards for particulate matter. The current federal and California standards are listed below:

TABLE I-4

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 $\mu g/m^3$
PM 2.5 24-Hour Average	35 $\mu g/m^3$	--
PM 2.5 Annual Average	15 $\mu g/m^3$	12 $\mu g/m^3$

Short-Term Exposure Effects

Epidemiological studies have provided evidence for most of the effects listed above. An association between increased daily or several-day-average concentrations of PM10 and excess mortality and morbidity is consistently reported from studies involving communities across the U.S. as well as in Europe, Asia, and South America. A review and analysis of epidemiological literature for acute adverse effects of particulate matter was published by the American Thoracic Society in 1996. Several adverse effects were listed as associated with daily PM10 exposures, as listed in Table I-5. It also appears that individuals who are elderly or have preexistent lung or heart disease are more susceptible than others to the adverse effects of PM10 (ATS, 1996).

Since then many more recent studies have confirmed that excess mortality and morbidity are associated with short term particulate matter levels (Pope, 2006).

Estimates of mortality effects from studies of PM10 exposures range from 0.3 to 1.7% increase for a 10 $\mu g/m^3$ increase in PM10 levels. The National Morbidity, Mortality, and Air Pollution Study (NMMAPS), a study of 20 of the largest U.S. cities, determined a combined risk estimate of about a 0.5% increase in total mortality for a 10 $\mu g/m^3$ increase in PM10 (Samet, 2000a). This study also analyzed the effects of gaseous co-pollutants. The results indicated that the association of PM10 and mortality were not confounded by the presence of the gaseous pollutants. When the gaseous pollutants were included in the analyses, the significance of the PM10 estimates remained. The PM10 effects were reduced somewhat when O_3 was also considered and tended to be variably decreased when NO_2, CO, and SO_2 were added to the analysis. These results argue that the effects are likely due to the particulate exposures; they cannot readily be explained by coexisting weather stresses or other pollutants.

TABLE I-5

Combined Effect Estimates of Daily Mean Particulate Pollution (PM10)

	% CHANGE IN HEALTH INDICATOR PER EACH 10 $\mu g/m^3$ 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

(Source: American Journal of Respiratory and Critical Care Medicine, Vol. 153, 113-50, 1996)

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

Studies of short term exposures to PM2.5 have also ~~find~~ found associations with ~~elevated~~ increases in mortality. The NMMAPS study conducted a national analysis of PM2.5 mortality association for 1999-2000. The risk estimates were 0.29% for all-cause ~~mortalityand~~mortality and 0.38% for cardio-respiratory mortality (Dominici. 2007). In its recent review EPA determined ~~The estimates~~that estimates for PM2.5 generally are in the range of ~~2.0~~0.29 to ~~8.5~~1.21% increase in total deaths per ~~25~~ 10 µg/m^3 increase in 24-hour PM2.5 levels. The estimates for cardiovascular related mortality range from ~~3.0~~0.03 to ~~7.0~~1.03% per ~~25~~ 10 µg/m^3 ~~,~~, and ~~24-hour PM2.5, and~~ for respiratory mortality estimates range from ~~2.0~~ 1.01to ~~7.0~~2.2% per ~~25~~ 10 µg/m^3 24-hour PM2.5 (EPA,2009).

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. ~~Other studies in Mexico City and Santiago, Chile reported that PM10-2.5 was as important as PM2.5. Overall effects estimates for PM10-2.5 fall in the range of 0.5 to 6.0 % excess mortality per 25 µg/m^3 24-hour average.~~ In the EPA review, (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 difference by season and climate area.

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

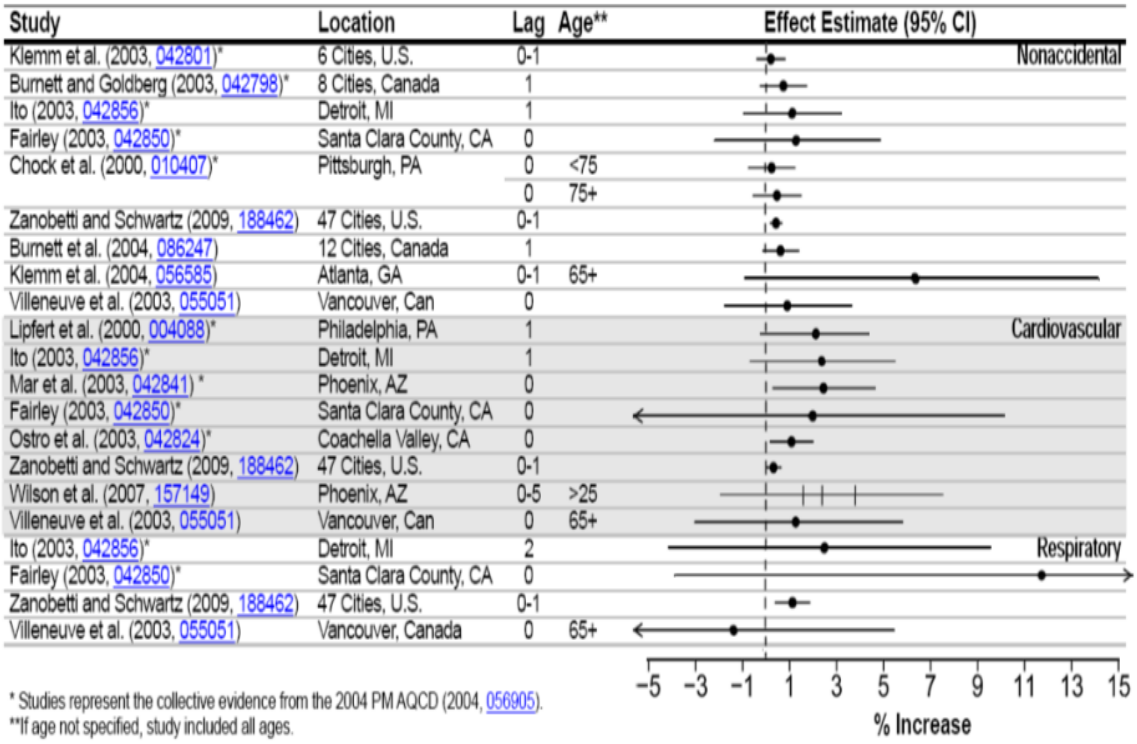


Figure 2~~2222~~

Summary of percent increase in total (nonaccidental) and cause-specific mortality per 10 µg/m3 increase in PM10-2.5

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 effects estimates are generally higher than the effects for mortality. The effects are associated with measures of PM10 and PM2.5. Effects are also associated with PM10-2.5. ~~Thus, it appears that when a relatively small number of people experience severe effects, larger numbers experience milder effects, which may relate either to the coarse or to the fine fraction of airborne particulate matter.~~

In the NMMAPS study, hospital admissions for those 65 years or older were assessed in 14 cities. Several models were compared to estimate associations of hospital admissions for specific disease categories and short term PM10 levels. Hospital admissions ~~for these individuals~~ showed an increase ranging from 0.68 – 1.47% for cardiovascular ~~dieases~~diseases, a range of 1.46 – 2.88% increase for chronic

obstructive pulmonary disease, and a ~~reange~~range of 1.31 – 2.86% increase for pneumonia ~~of 6% for cardiovascular diseases and a 10% increase for respiratory disease admissions,~~ per 1~~5~~0 µg/m^3 increase in PM10. (Samet, 2000) In the reanalysis of the study~~,~~(, (HEI 2003), it was found that using different models the pollution coefficients were on average lower. However the authors note that most of the conclusions of associations with PM10 exposures and hospital admissions held.~~The excess risk for cardiovascular disease ranges from 3-10% per 50 µg/m^3 PM10 and from 4-10% per 25 µg/m^3 PM2.5 or PM10-2.5.~~

Similarly, school absences, lost workdays and restricted activity days have also been used in some studies as indirect indicators of acute respiratory conditions. The results are suggestive of both immediate and delayed impact on these parameters following elevated particulate matter exposures. These observations are consistent with the hypothesis that increased susceptibility to infection follows particulate matter exposures, which is consistent with mechanistic studies that show PM exposures may suppress the immune system.

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% ~~3% to 42%~~ for medical visits for respiratory illnesses was found corresponding to a ~~50~~ 10 µg/m^3 change in PM10. A ~~limited~~ 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 (EPA, 2009).

The biological mechanisms by which particulate matter can produce health effects are being investigated in laboratory studies. Inflammatory responses in the respiratory system in humans and animals exposed to concentrated ambient particles have been measured. These include effects such as increases in neutrophils in the lungs. Other changes reported include increased release of cytokines and interleukins, chemicals released as part of the inflammatory process. The effects of particulate

matter may be mediated in part through the production of reactive oxygen species during the inflammatory process. ~~Recent~~ Several reviews discuss mechanistic studies in more detail (Brunekreef, 2002; Brook, 2004, Brook, 2010).

Long-Term Exposure Effects

While most studies have evaluated the acute effects, some studies specifically focused on evaluating the effects of chronic exposure to PM10 and PM2.5. Studies have analyzed the mortality of adults living in different U.S. cities. After adjusting for important risk factors, taken as a whole these studies found a positive association of deaths and exposure to particulate matter. A similar association was observable in both total number of deaths and deaths due to specific causes. The largest effects were observed from cardiovascular causes and ischemic heart disease. A shortening of lifespan was also reported in these studies.

Since the initial promulgation by EPA of the National Ambient Air Quality Standards for PM2.5, controversy has remained over the association of mortality and exposures to PM2.5. Thus an expanded discussion of ~~these studies~~this issue is presented below.

Significant associations for PM2.5 for both total mortality and cardiorespiratory mortality were reported in a study following a national cohort recruited by the American Cancer Society for ~~a~~ its Cancer Preventions Study II over several years. A re-analysis of the data from this study confirmed the initial finding (Krewski, 2000). In this study, mortality rates and PM2.5 levels were analyzed for 51 metropolitan areas of the U.S. Average levels from monitors in each area were used to estimate exposures. At these levels of aggregation, regional differences in the association of PM2.5 and mortality were noted, with higher associations in the Northeast, and lower or non-significant associations in the West.

The Harvard Six Cities Study evaluated several size ranges of particulate matter and reported significant associations with PM15, PM2.5, sulfates, and non-sulfate particles, but not with coarse particles (PM15 – PM2.5). An extension of the Harvard Six Cities Cohort confirmed the association of mortality with PM2.5 levels (Laden, 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 compounds. An update to this study covering a follow-up over the years 1974 to 2009 (Lepeule, 2012) was recently published. 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.

A recent study conducted in Canada on long term particulate exposures and mortality found a 15% increase in all-cause mortality and a 31 % increase in ischemic heart disease mortality for a 10 $\mu g.m^3$ increase in PM2.5. The mean concentration among all study subjects was 8.7 $\mu g/m^3$ (Crouse, 2012)

A follow-up study of the American Cancer Society cohort confirmed and extended the findings in the initial study. The researchers estimated that, on average, a 10 µg/m3 increase in fine particulates was associated with approximately a 4% increase in total mortality, a 6% increase in cardiopulmonary mortality, and an 8% increase risk of lung cancer mortality (Pope, 2002). The magnitude of effects is larger in the long-term studies than in the short-term investigations. In an additional re analysis and extension of the American Cancer Society cohort from 1982 to 2000 (Krewski, 2009), and including additional metropolitan areas for the most recent years, effects estimates on mortality were similar, though somewhat higher, than those reported previously.

Other national studies include an analysis of mortality and PM2.5 exposures in a Medicare population. Zeger and Associates (2008) assembled a Medicare cohort by including all Medicare enrollees residing in zip codes with centroids within 6 miles of a PM2.5 monitor. PM2.5 data was obtained from the monitoring stations, and mean annual levels were called for the zip codes within six miles of each monitor. The estimated associations between exposures to PM2.5 and mortality for the eastern and central portions of the U.S were similar to those previously published in the Six Cities Study and the American Cancer Society cohorts. The authors reported that there were no significant associations between zip code levels of PM2.5 and mortality rates in the western region of the U.S. This lack of association 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 these counties. The authors further reported that they found no associations of PM2.5 with mortality in persons aged 85 years or higher.

Analyses of mortality and PM2.5 levels specific to California have also been reported. A cohort of elderly individuals (average age of 65 yr in 1973) recruited from 11 California counties was followed over several years (Enstrom, 2005). An association for exposure with all cause deaths was reported from 1973–1982. However, no significant association was found in the later time period of 1983–2002.

Pollutant levels were taken from ambient monitors and averaged over each county to estimate exposures.

~~Two analyses of the American Cancer Society cohort 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. Using data from monitoring stations in the Los Angeles area, one study applied interpolation methods (Jerrett, 2005) and another applied land use regression techniques (Krewski, 2009) to estimate exposures to the study individuals. Significant associations of PM2.5 with mortality from all causes and cardiopulmonary disease were reported, with the magnitude of risks being up to three times higher than those from the national studies of the American Cancer Society cohort. This provides evidence that using methods to provide more detailed exposure estimates can result in stronger associations of PM2.5 and mortality.~~

Two recent reports have been released looking at air pollution and health effects in California. One study (Lipsett, 2011) followed school teachers recruited in 1995, and followed through 2005. Pollutant exposures at the subject residence were estimated using data from ambient monitors, and extrapolated using a distance weighted method. The authors reported significant association of PM2.5 levels and mortality from ischemic heart disease, but no associations were found with all cause, cardiovascular, or respiratory disease.

The second study (Jerrett, 2011) followed individuals in California from the American Cancer Society cohort recruited starting in 1982, with follow up to 2000. Pollutant levels at subject residences were estimated using several methods. All but one of the methods found no association of all-cause mortality with PM2.5 levels. All exposure estimation methods were reported to have found significant associations with ischemic heart disease mortality, however. The authors noted that mortality rates differ in urban areas compared to non-urban areas, and so included a variable for this in a land use regression model to estimate effects on mortality. When the authors applied the land use regression model including an urban indicator to estimate exposures, all-cause mortality, mortality from cardiovascular disease, and mortality from ischemic heart disease were all significantly associated with PM2.5 levels.

Some other studies have focused on particulate matter exposure and health have also focused on potential health effects in residents of Southern California. Two analyses of the American Cancer Society cohort, for example~~, focused~~, 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. Using data from monitoring stations in the Los Angeles area, one study applied interpolation methods (Jerrett, 2005) and another applied land use regression techniques (Krewski, 2009) to estimate exposures to the study individuals. Significant associations of PM2.5 with mortality from all causes and cardiopulmonary disease were reported, with the magnitude of risks being up to three times higher than those from the national studies of the American Cancer Society cohort. This provides evidence that using methods to provide more detailed exposure estimates can result in stronger associations of PM2.5 and mortality.

Another study looked at measuring of atherosclerosis in Southern California residents Kunzli, 2005). An assessment of the carotid intima-media thickness (CIMT) was used as a measure of subclinical atherosclerosis. 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 U.S. EPA has recently proposed to lower the annual National Ambient Air Quality Standard for PM2.5 (U.S. EPA, 2012a). EPA also released a Regulatory Impact Analysis (U.S. EPA 2012b~~)which~~) which looked at the costs and benefits of alternate PM2.5 stand levels. As part of the analysis, EPA also looked at California specific studies regarding PM2.5 and mortality published in the scientific literature. The 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 EPAs judgment the California related studies provided estimates of mortality consistent with or higher than those from the national studies.

Other studies report evidence indicating that particulate matter exposure early in pregnancy may be associated with lowered birth weights (Bobak, 1999). Studies from the U.S., the Czech Republic and Mexico City have reported that neonatal and early postnatal exposure to particulate matter may lead to increased infant mortality. A more recent study in Southern California found increased risks for infant deaths

associated with exposures to particulates and other pollutants (Ritz, 2006). These results suggest that fetuses and infants may be ~~a~~ subgroups affected by particulate matter exposures.

In addition, some long-term effect studies have reported an increased risk of mortality from lung cancer associated with particulate matter exposures. A study involving California Seventh Day Adventists (very few of whom smoke) has reported an association of lung cancer mortality with PM10 levels. It is not clear from these studies whether the association relates to causation of disease, or whether individuals with cancer are more susceptible to other effects of particles leading to the observed mortality association. A study that followed a large number of individuals living in the largest U.S. cities found elevated lung cancer risk associated with long-term average PM2.5 levels (Pope, 2002).

Several studies have assessed the effects of long-term particulate matter exposure on respiratory symptoms and lung function changes. Associations have been found with symptoms of chronic bronchitis and decreased lung function. A study of school children in 12 communities in Southern California showed significant association of particulate matter with bronchitis or phlegm in children with asthma. These effects were also associated with NO_2 and acid vapor levels (McConnell, 1999).

A cohort of fourth graders from the Southern California communities was followed over a period of four years by the Children's Health Study. A lower rate of growth in lung function was found in children living in areas with higher levels of particulate pollution (Gauderman, 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, 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 regain some of the lung function growth rate (Avol, 2001). By the time the fourth graders graduated from high school, a significant number showed lower lung function. The risk of lower lung function was about five times higher in children with the highest PM2.5 exposure when compared to the

lowest exposure communities (Gauderman, 2004). These deficits are likely to persist since the children were at the end of their growth period.

Despite data gaps, the extensive body of epidemiological studies has both qualitative and quantitative consistency suggestive of causality. A considerable body of evidence from these studies suggests that ambient particulate matter, alone or in combination with other coexisting pollutants, is associated with significant increases in mortality and morbidity in a community.

In summary, the scientific literature indicates that an increased risk of mortality and morbidity is associated with particulate matter at ambient levels. 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.

EPA staff has presented conclusions on the particulate matter causal determination of several health effects based on a recent review of the available scientific studies (EPA, 2009). These are depicted in the Tables below.

TABLE I-6

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

SHORT-TERM EXPOSURES	
Health Outcome	**Causality Determination**
Cardiovascular effects	Suggestive
Respiratory effects	Suggestive
Mortality	Suggestive

LONG-TERM EXPOSURES	
Health Outcome	**Causality Determination**
Cardiovascular effects	Inadequate
Respiratory effects	Inadequate
Mortality	Inadequate
Reproductive and developmental	Inadequate

From EPA, 2009

TABLE I-76

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

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

From EPA, 2009

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. The most recent assessment focused on premature mortality and PM2.5 (CARB 2010). The analysis used the EPA's risk assessment methodology for calculating premature mortality, and used ambient air quality measurements averaged over a three year period of 2006-2008. The analysis indicated that PM2.5 related premature deaths in California

as 9,200 with an uncertainty range of 7,300 – 11,000. Estimates were also made at for the California Aair Basins. For the South Coast Air Basin, the estimate was 4,900 with an uncertainty range of 3,900 – 6,000. These estimates were calculated using the associations of cardiopulmonary mortality and PM2.5 from the second exposure period from Krewski (2009). The associations from the first exposure period from Krewski, 2009 as well as other cause of death estimates were also presented.

Another analysis of health impacts in the South Coast was conducted as part of the Draft Socioeconomic Report for the 2012 AQMP. The analysis estimates the anticipated costs and benefits of adopting the measures in the Draft 2012 AQMP. Adopting these measures is projected to result in attainment of the national PM2.5 standards by 2014, and attainment of the national Ozone standard by 2023. The total average annual quantifiable benefits associated with implementing the Draft 2012 AQMP were calculated and represent the currently quantifiable benefit of moving beyond today's regulations to the level needed to meet the federal PM2.5 standards. The table below shows the number of avoided cases (or person-days) by health effect when the Basin attains the PM2.5 standard in 2014 and also in 2023 that result (SCAQMD 2012).

TABLE I-8

Changes in Number of Health Effects for Future Years*
for Measures contained in the Draft 2012 AQMP

Health Outcome	Number of Avoided Cases	
	2014	2023
Mortality	668	275
Acute Bronchitis	597	186
Non-Fatal Heart Attacks	29 - 261	12 – 105
Lower & Upper Respiratory Symptoms	18,384	5,750
Emergency Room Visits	153	53
Hospital Admissions	151	62
Minor Restricted Activity Days	287,447	95,093
Work Loss Days	48,805	16,055
Asthma Attacks	26,910	3,628

*Changes reflect differences in base and control cases for a given year. Positive numbers are reductions in symptoms due to the Draft 2012 AQMP.

**Person-days.

ULTRAFINE PARTICLES

As noted above, numerous studies have found association of particulate matter levels with adverse effects, including mortality, hospital admissions, and respiratory disease symptoms. The vast majority of these studies used particle mass of PM10 or PM2.5 as the measure of exposure. Some researchers have postulated, however, that ultrafine particles may be responsible for some of the observed associations of particulate matter and health outcomes (Oberdorster, et al, 1995; Seaton, et al, 1995). Ultrafine particles ~~are generally classified of 0.1 µm and small diameter~~ that have aerodynamic diametes of less than 0.1 µm..

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

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

Smaller particles can also be inhaled deep into the lungs. As much as 50% of 0.02 µm diameter particles are estimated to be deposited in the alveolar region of the lung. There is complex nature of the relation between deposition and particle size. The ultrafine particles generally have higher fractional deposition in the alveolar region. However, for the smaller nucleation mode (particles less than 0.01 µm size) the deposition in the alveolar region declines, but increases in the extrathoracic region.

Exposures of laboratory animals to ultrafine particles have found cardiovascular and respiratory effects. Using an animal model of atherosclerotic disease, m~~M~~ice exposed to concentrated ~~near roadway~~ ultrafine particles near a roadway in Southern California showed larger early atherosclerotic lesions than mice exposed to ~~concertrated~~concentrated PM2.5 or to filtered air (Araujo, 2008). In a mouse allergy model, exposures to concentrated ultrafine particles resulted in a greater response to

antigen challenge to ovalbumin (Li, 2010), indicating that vehicular traffic exposure could exacerbate allergic inflammation in already-sensitized animals.

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, 2011, for example found exposure to diesel exhaust particulate attenuated both acetylcholine and sodium-nitroprusside -induced vasorelaxation.

There are no long-term studies of human population exposure to ultrafine particle, as there is a lack of a monitoring network in the U.S. There have been several cross sectional epidemiological studies of ultrafine particles, mainly from Europe. Some of these studies found effects on hospital admissions, emergency department visits, for respiratory and cardiovascular effects. Other studies, however, have not found such effects (EPA, 2009). Concentrations of ultrafine particles can vary geographically, and it is not clear how well central site monitors may capture actual exposures.

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 (EPA, 2009). These are depicted in the table below.

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

TABLE I-~~8~~9~~7~~

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

SHORT-TERM EXPOSURES	
Health Outcome	**Causality Determination**
Cardiovascular effects	Suggestive
Respiratory effects	Suggestive
Central nervous system	Inadequate information to assess
Mortality	Inadequate

LONG-TERM EXPOSURES	
Health Outcome	**Causality Determination**
Cardiovascular effects	Inadequate
Respiratory effects	Inadequate
Mortality	Inadequate
Reproductive and developmental	Inadequate
Cancer, Mutagenicity, Genotoxicity	Inadequate

From EPA, 2009

CARBON MONOXIDE

The high affinity of carbon monoxide (CO) to bond with oxygen-carrying proteins (hemoglobin and myoglobin) results in reduced oxygen supply in the bloodstream of exposed individuals. The reduced oxygen supply 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 (U.S. EPA, 2000, 2010).

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). Exposure to CO is often evaluated in terms of COHb levels in blood measured as percentage of total hemoglobin bound to CO. COHb levels in non-smokers range between 0.3 and 0.7% and 5 to 10% in smokers. COHb levels in excess of 1.5% in a significant proportion of urban non-smoking populations can be considered as evidence of widespread exposure to environmental CO.

Under controlled laboratory conditions, healthy subjects exposed to CO sufficient to result in 5% COHb levels exhibited reduced duration of maximal exercise performance and consumption of oxygen. Studies involving subjects with coronary artery disease who engaged in exercise during CO exposures have shown that COHb

levels as low as 2.4% can lead to earlier onset of electrocardiograph changes indicative of deficiency of oxygen supply to the heart. Other effects include an earlier onset of chest pain, an increase in the duration of chest pain, and a decrease in oxygen consumption.

Findings of epidemiologic studies have observed associations between ambient CO concentration and emergency department visits and hospital emissions for ischemic heart disease and other cardiovascular diseases.

Animal studies associated with long-term exposure to CO resulting in COHb levels that are equivalent to those observed in smokers have shown indication of reduction in birth weight and impaired neurobehavior in the offspring of exposed animals.

Epidemiological studies conducted in Southern California have indicated an association with CO exposure during pregnancy to increases in pre-term births (Ritz, 2000). However, the results were not consistent in different areas studied. The increase in the pre-term births was also associated with PM10 levels. Another study found increased risks for cardiac related birth defects with carbon monoxide exposure in the second month of pregnancy (Ritz, 2002). Toxicological studies in laboratory animals with higher than ambient levels of CO have also reported decrements in birth weight and prenatal growth.

EPA staff has presented conclusions on causal determination of the health effects of carbon monoxide based on a recent review of the available scientific studies (EPA, 2010). These are depicted in the table below.

TABLE I-~~9~~108

Causal Determination for Health Effects of Carbon Monoxide

SHORT-TERM EXPOSURES	
Health Outcome	**Causality Determination**
Cardiovascular morbidity	Likely to be a causal relationship
Central nervous system	Suggestive
Respiratory morbidity	Suggestive
Mortality	Suggestive
LONG-TERM EXPOSURES	
Health Outcome	**Causality Determination**
Cardiovascular morbidity	Inadequate

Central nervous system	Suggestive
Birth outcomes and developmental effects	Suggestive
Respiratory morbidity	Inadequate
Mortality	Not likely to be a causal relationship

From EPA, 2010

NITROGEN DIOXIDE

The U.S. EPA has recently reviewed the health effects of nitrogen dioxide (U.S. EPA, 2008a). Evidence for low-level nitrogen dioxide (NO_2) exposure effects is derived from laboratory studies of asthmatics and from epidemiological studies. Additional supportive evidence is derived from animal studies.

Some e~~E~~pidemiological studies using the presence of an unvented gas stove as a surrogate for indoor NO_2 exposures suggest an increased incidence of respiratory infections or symptoms in children. However the evidence is mixed.

Recent studies related to outdoor exposure have found health effects associated with ambient NO_2 levels, including respiratory symptoms, respiratory illness, decreased lung function, increased emergency room visits for asthma, and cardiopulmonary mortality. However, since NO_2 exposure generally occurs in the presence of other pollutants, such as particulate matter, these studies are often unable to determine the specific role of NO_2 in causing effects.

The Children's Health Study in Southern California found associations of air pollution, including NO_2, PM10, and PM2.5, with respiratory symptoms in asthmatics (McConnell, 1999). Particles and NO_2 were correlated, and effects of individual pollutants could not be discerned. A subsequent analysis indicated a stronger role for NO2 (McConnell, 2002).

Ambient levels of NO_2 were also associated with a decrease in lung function growth in a group of children followed for eight years. In addition to NO_2, the decreased growth was also associated with particulate matter and airborne acids. The study authors postulated ~~that~~ this ~~these~~ may be a result ~~measure~~ of a package of pollutants from traffic sources (Gauderman, 2004).

Results from controlled exposure studies of asthmatics demonstrate an increase in the tendency of airways to contract in response to a chemical stimulus (bronchial reactivity) or after inhaled allergens. Effects were observed with exposures from 0.1 to 0.3 ppm NO_2 for periods ranging from 30 minutes to 3 hours. A similar response is reported in some studies with healthy subjects at higher levels of exposure (1.5 - 2.0 ppm). Mixed results have been reported when people with chronic obstructive lung disease are exposed to low levels of NO_2.

Short-term controlled studies of animals exposed to NO_2 over a period of several hours indicate cellular changes associated with allergic and inflammatory response and interference with detoxification processes in the liver. In some animal studies

the severity of the lung structural damage observed after relatively high levels of short-term ozone exposure is observed to increase when animals are exposed to a combination of ozone and NO_2.

In animals, longer-term (3-6 months) repeated exposures at 0.25 ppm appear to decrease one of the essential cell-types (T-cells) of the immune system. Non-specific changes in cells involved in maintaining immune functions (cytotoxic T-cells and natural killer cells) have been observed in humans after repeated exposure (4-6 days) to >0.6 ppm of NO_2 (20 min. - 2 hours). All these changes collectively support the observation reported both in population and animal studies of increased susceptibility to infections, as a result of NO_2 exposure.

The U.S. EPA recently adopted a new short-term standard of 100 ppb (0.1 ppm) averaged over 1 hour. The standard was designed to protect against increases in airway reactivity in individuals with asthma observed in controlled exposure studies, as well as respiratory symptoms observed in epidemiological studies.

SULFUR DIOXIDE

Controlled laboratory studies involving human volunteers have clearly identified asthmatics as ~~the most~~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 significant alteration of lung function, such as increases in airway resistance and decreases in breathing capacity. In some, the exposure can result in severe symptoms necessitating the use of medication for relief. The response to SO_2 inhalation is observable within 2 minutes of exposure, increases further with continuing exposure up to 5 minutes then remains relatively steady as exposure continues. SO_2 exposure is generally not associated with any delayed reactions or repetitive asthmatic attacks.

In epidemiologic studies, associations of SO_2 levels with increases in respiratory symptoms, increases in emergency department visits and hospital admissions for respiratory-related causes have been reported. Coupled with the human clinical studies, these data suggest that SO_2 can trigger asthmatic episodes in individuals with pre-existing asthma.

The U.S. EPA has recently revised the SO_2 air quality standard. The previous 24-hour standard was rescinded and replaced with a new 1-hour standard at 75 ppb (0.075 ppm) to protect against ~~high short term exposures~~acute asthma attacks in sensitive individuals.

Animal studies have shown that despite SO_2 being a respiratory irritant, it does not cause substantial acute or chronic toxicity in animals exposed at ambient concentrations. However, relatively high exposures (10 ppm of SO_2 for 72 hours) in mice can lead to tissue damage, fluid accumulation and sloughing of respiratory lining. Sensitization to allergies is observable in guinea pigs repeatedly exposed to high levels (72 ppm) of SO_2. This effect needs further evaluation in clinical and population studies to identify any chronic exposure impact on both asthmatic incidence and attacks in a population.

Some epidemiological studies indicate that the mortality and morbidity effects associated with the fine fraction of particles show a similar association with ambient SO_2 levels. In these studies, efforts to separate the effects of SO_2 from fine particles have not been successful. Thus, it is not clear whether the two pollutants act synergistically, or whether being generated from similar combustion sources, they represent the same pollution index for the observed effects.

SULFATES

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.

In recent years, a vast majority of effects (mortality and morbidity) associated with fine particles (PM2.5) and sulfur dioxide have shown a similar association with ambient sulfate levels in some population studies. The efforts to fully separate the effects of sulfates from other coexisting pollutants have not been successful. This may be due to the fact that these pollutants covary under ambient conditions, having been emitted from common sources; and the effects observed may be due to the combination of pollutants, rather than a single pollutant.

A clinical study involving exposure of human subjects to sulfuric acid aerosol indicated that adolescent asthmatics may be a susceptible population subgroup with some changes in lung function observed with exposures below 100 $\mu g/m^3$. In

general, however, laboratory exposures of human volunteers to sulfates at or near ambient levels have not found significant changes in lung function.

Results from animal studies involving exposures to sulfuric acid aerosol, ammonium bisulfate and ammonium sulfate indicate that acidic particles (former two) are more toxic than non-acidic particles (latter). In addition, the severity or magnitude of both mortality and morbidity effects is relatively higher in population studies of the eastern United States and Canada where sulfate concentrations are higher than for those observed in the western United States. Mixed results have been reported from studies which attempted to ascertain the role of acidity in determining the observed toxicity.

LEAD

The U.S. EPA has recently reviewed the health effects of ambient lead exposures in conjunction with a review of the NAAQS for lead. (U.S. EPA 2006b; U.S. EPA 2007b). The following summary is taken from these reviews.

There are a number of potential public health effects at low level exposures. The health implications are generally indexed by blood lead levels, which are related to lead exposures both from inhalation as well as from ingestion. As identified by EPA, effects ~~includeimpacts~~include impacts on population IQ, as well as heart disease and kidney disease. The array of health effects includes the following.

- Heme biosynthesis and related functions;
- Neurological development and function;
- Reproduction and physical development;
- Kidney function;
- Cardiovascular function
- Immune function

Children appear to be sensitive to the neurological toxicity of lead, with effects observed at blood lead concentration ranges of 5 – 10 µg/dL, or possibly lower. No clear threshold has yet been established for such effects.

According to the 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.

EPA has recently revised the NAAQS for lead to a level of 0.15 µg/m^3 averaged over a rolling 3 month period to protect against lead toxicity. The following two charts, taken from the U.S. EPA review, depict the health effects of lead in relation to blood levels.

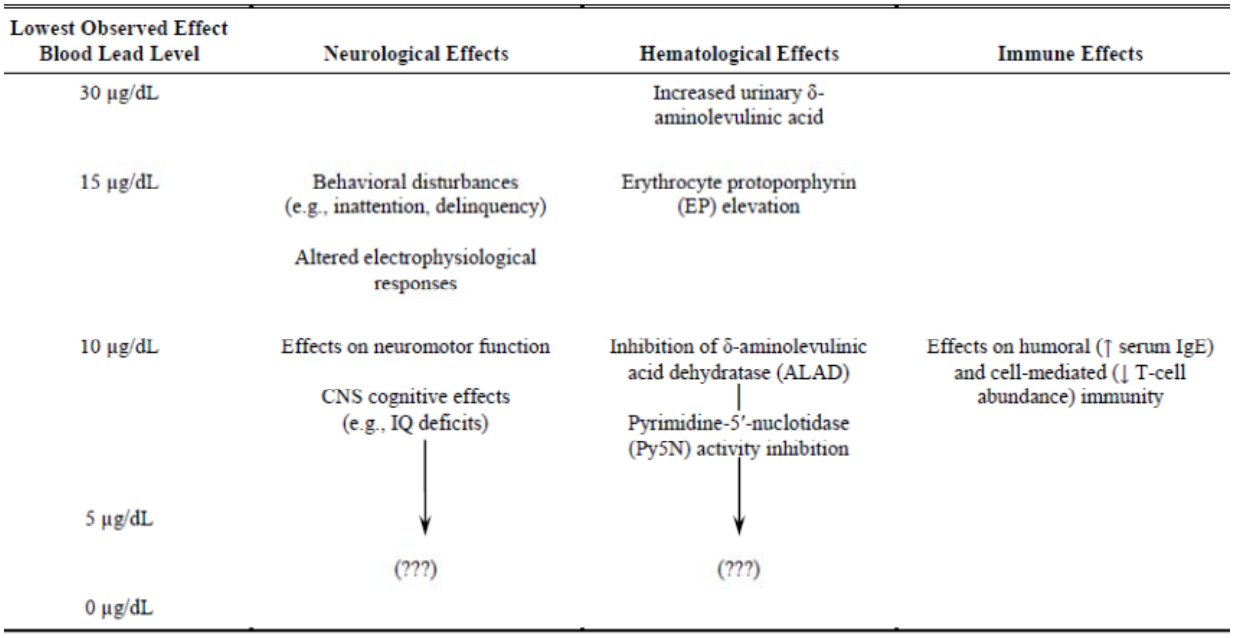


FIGURE I-~~333332~~

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

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				

FIGURE I-~~44444~~3

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

TOXIC AIR CONTAMINANTS

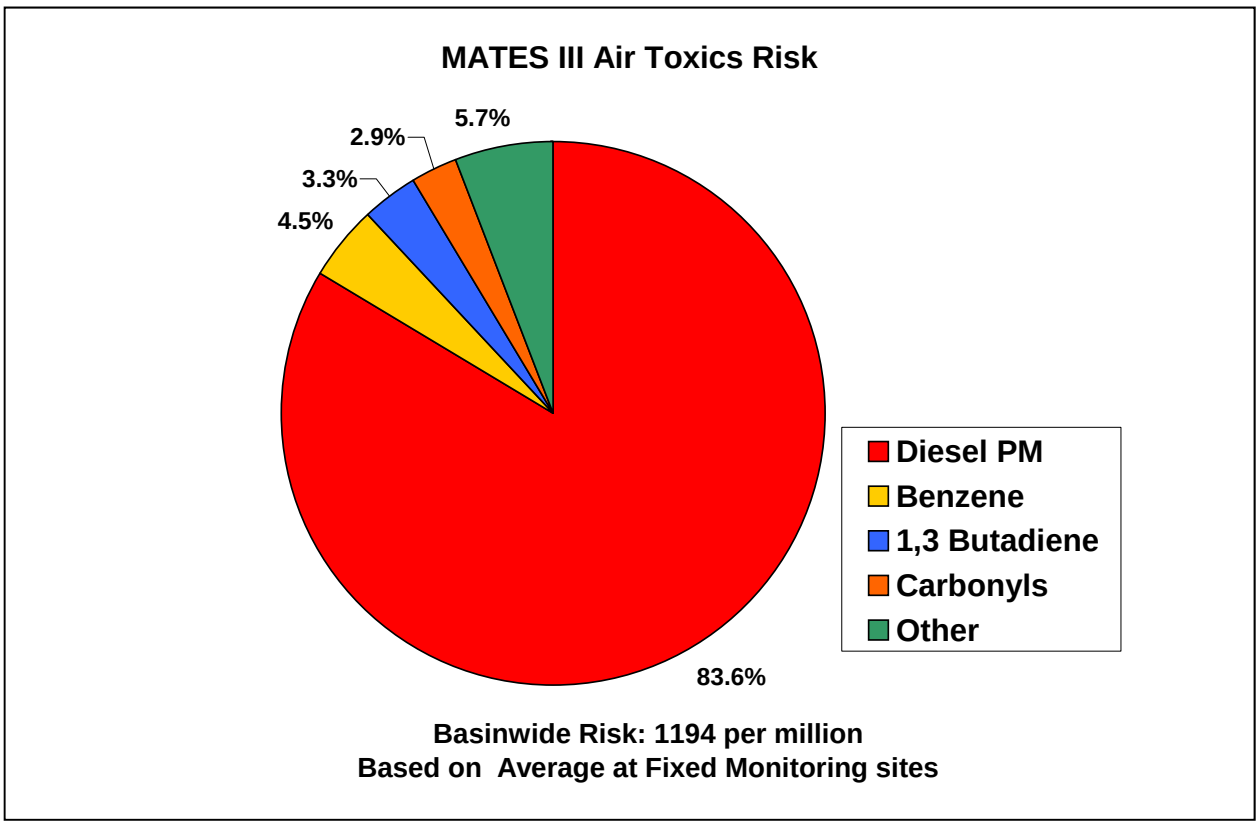
Toxic air contaminants are pollutants for which there generally are no ambient air quality standards. Under California's Air Toxics Program, CARB staff and Office of Environmental Health Hazard Assessment (OEHHA) assess the health effects of substances that may pose a risk of adverse health effects. These effects are usually an increased risk for cancer, ~~or~~ adverse birth outcomes and 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.

~~CARB and~~ 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.

The District conducted studies on the ambient concentrations and estimated the potential health risks from air toxics (SCAQMD, 2008). In the latest study, a two

year monitoring program was undertaken at 10 sites throughout the SCAB over the time period 2004-2006. Over 30 substances were measured, and annual average levels were calculated. The results showed that the overall risk for excess cancer from a 70-year lifetime exposure to the levels of air toxics calculated as the average level at the 10 sites was about 1,200 in a million. The largest contributor to this risk was diesel particulate matter, accounting for about 84% of the air toxics risk. A breakdown of the major contributors to the air toxics risk is shown in the figure below~~FIGURE I-4~~.

While the California Air Resources Board listed Diesel Particulate Matter as a Toxic Air Contaminant in 19~~88~~89. ~~, t~~The International Agency for Research on Cancer, an arm of the World Health Organization, classified diesel exhaust ~~as probably~~as probably carcinogenic to humans. ~~r~~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 cancer in humans (Benbrahim-Tallaa, 2012).



~~FIGURE I-4~~FIGURE I-5

Major Pollutants Contributing to Air Toxics Cancer Risk in the South Coast Air Basin

For non-cancer health effects, OEHHA has developed acute and chronic Reference Exposure Levels (RELs). RELs are concentrations in the air below which adverse health effects are not likely to occur. Acute RELs refer to short-term exposures, generally of one-hour duration. Chronic RELs refer to long-term exposures of several years. OEHHA has also established 8-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. The measured levels from the most recent study were below the applicable Reference Exposure Levels.

The key air toxics contributing to risk from mobile and stationary sources are listed in TABLE I-9.

TABLE I-1109

Key Toxic Air Contaminants in the SCAB

MOBILE SOURCES	STATIONARY SOURCES
Acetaldehyde	Hexavalent Chromium
Benzene	Methylene Chloride
1,3 Butadiene	Nickel
Diesel Particulate Matter	Perchloroethylene
Formaldehyde	Trichloroethylene

CONCLUSION

A large body of scientific evidence shows that the adverse impacts of air pollution in 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, earlier mortality.

As the scientific methods for the study of air pollution health effects has progressed over the past decades, adverse effects have been shown to occur at lower levels of exposure. For some pollutants, no clear thresholds for effects have been demonstrated. The new findings have, in turn, led to the revision and lowering of National Ambient Air Quality Standards which, in the judgment of the Administrator of the U.S. EPA, are necessary to protect public health. The figures below are meant to convey some of the historical context to recent revisions to the NAAQS for ozone and for particulate matter.

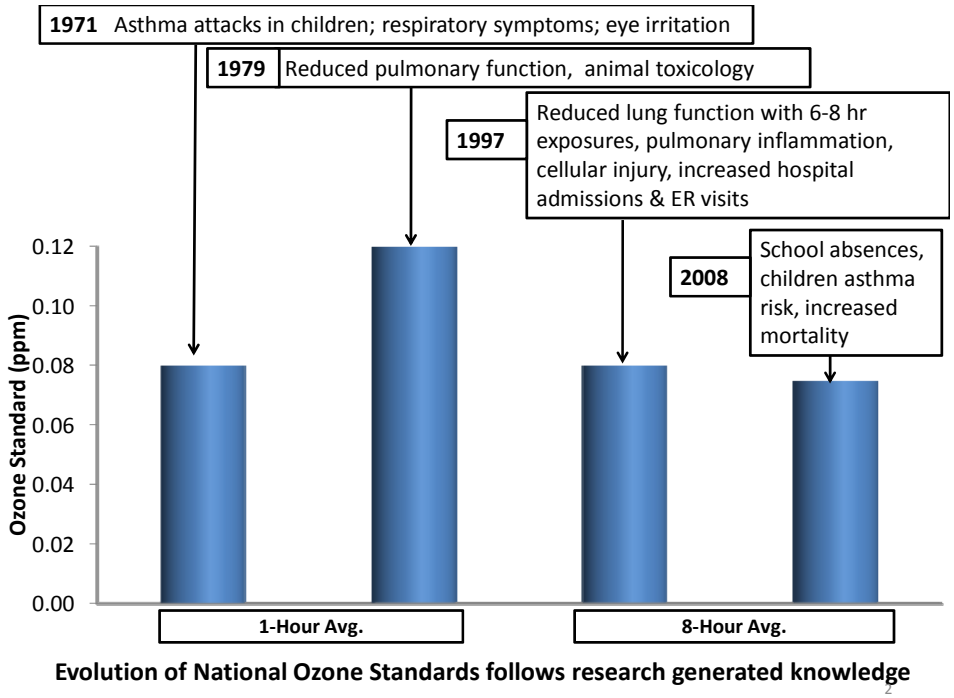


FIGURE I-~~666~~654

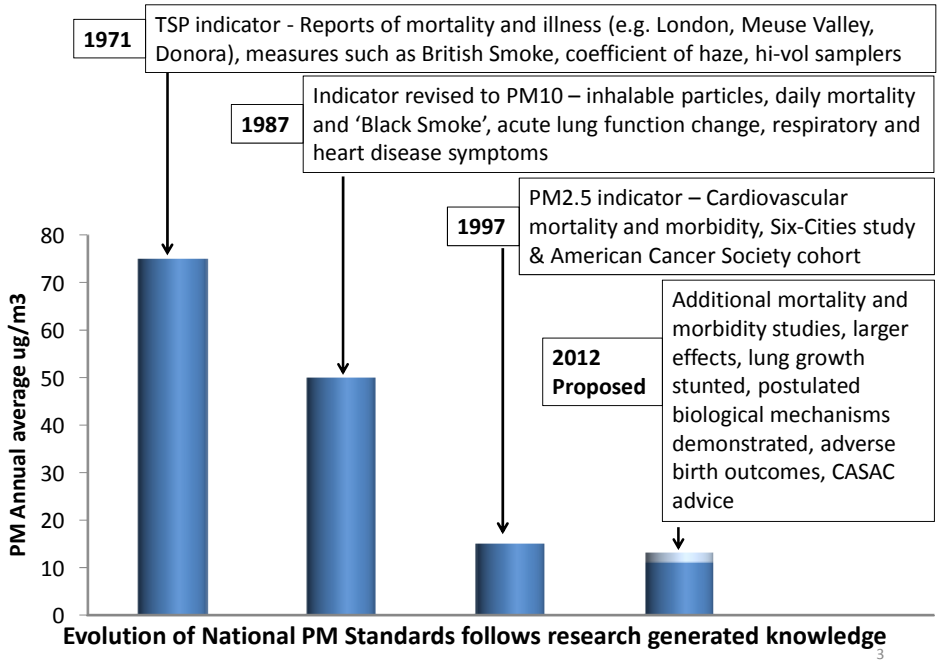


FIGURE I- ~~777~~765

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ATTACHMENT 1

ROSTER OF THE 2012 AQMP ADVISORY COUNCIL

South Coast AQMD Advisory Council
2012

NAME	AFFILIATION
Greg Adams	Los Angeles County Sanitation Districts
Todd Campbell	Clean Energy Fuels
David Czamanske	Sierra Club of Pasadena
Afif El-Hasan	American Lung Association
John Froines	UCLA School of Public Health
Ed Laird	Laird Coatings Corp
William LaMarr	Small Business Alliance
Julia Lester	ENVIRON
Rita Loof	RadTech
Robert McConnell	USC
J. Wayne Miller	CE-CERT Bourns College of Engineering
Emily Nelson	Consultant
Gary Polakovic	Make Over Earth
Walter Siembab	South Bay COG; Siembab Planning Associates
Sam Soret	Loma Linda University, School of Public Health
Mike Wang	WSPA

ATTACHMENT 2

CARB AND OEHHA COMMENTS

Appendix I-Health Effects was submitted to the following individuals for review and comment:

Linda Smith, Ph.D.
Chief, Health Exposure Assessment Branch
California Environmental Protection Agency
California Air Resources Board (CARB)

Melanie Marty, Ph.D.
Assistant Deputy Director
Scientific Affairs Division
Office of Environmental Health Hazard Assessment (OEHHA)

Copies of their comments follow.

CARB Comments on 2012 Appendix I-Health Effects

From: Smith, Linda@ARB [mailto:lsmith@arb.ca.gov]
Sent: Wednesday, September 26, 2012 1:40 PM
To: Jean Ospital
Cc: Herner, Jorn@ARB
Subject: RE: AQMD Advisory Council Update and Meeting on October 11, 2012

Jean,

Thank you for the opportunity to review and comment on Appendix I of the SC AQMP. Overall, it is a well-written document on the health effects of exposure to the major air pollutants, summarizing the most important literature in the field. Our comments, which are embedded in the document (attached), are brief. There are a few suggestions for improving clarity, and we noted a few minor errors in fact that should be corrected.

Please contact me if you have any questions, and thanks, again. I hope this email finds you well.

Regards,
Linda
* Linda Tombras Smith, Ph.D.
Chief, Health and Exposure Assessment Branch California Environmental Protection Agency Air Resources Board lsmith@arb.ca.gov
* *

The energy challenge facing California is real. Every Californian needs to take immediate action to reduce energy consumption. For a list of simple ways you can reduce demand and cut your energy cost, see our web site at http://www.arb.ca.gov

-----Original Message-----
From: Jean Ospital [mailto:JOspital@aqmd.gov]
Sent: Friday, September 21, 2012 8:34 AM
To: Afif El-Hasan (Afif.h.el-hasan@kp.org); David Czamanske (dczamanske@hotmail.com); Ed Laird (elaird@coatingsresource.com); Emily Nelson (dremilynelson@gmail.com); makeoverearth.com, gary; Greg Adams (gadams@lacsd.org); J. Wayne Miller (wayne.miller@ucr.edu); John Froines (jfroines@ucla.edu); Lester, Julia; Mike Wang (mwang@wspa.org); radtech.org, rita; Robert McConnell (rmcconne@usc.edu); Sam Soret (ssoret@llu.edu); Todd Campbell (tcampbell@cleanenergyfuels.com); Walter Siembab (ws@siembab.com); William LaMarr (BillLaMarr@msn.com)
Cc: Marty, Melanie@OEHHA; Smith, Linda@ARB; Elaine Chang; Philip Fine; Barbara Baird; William Wong; Marilyn Traynor; Christina Batteate
Subject: AQMD Advisory Council Update and Meeting on October 11, 2012

To: 2012 AQMD Advisory Council
RE: Update on Draft Appendix I Review

Greetings to all.

At the July 11, 2012 meeting of the Advisory Council the group requested that another meeting be held to review Appendix I and any revisions that might be made. We have scheduled a meeting of the Advisory Council for October 11, 2012. Details are below.

2012 AQMP Advisory Council meeting
October 11, 2012
10 am - noon
Room CC8
AQMD Offices
21865 Copley Drive,
Diamond Bar, CA

An interim updated draft has been posted to the AQMD website at http://www.aqmd.gov/aqmp/2012aqmp/RevisedDraft/AppI.pdf. Additions to the initial draft were made based on suggestions from the advisory group, and include a brief summary of lead health effects, an expansion of the conclusion section to reflect how health studies support revisions to the National Ambient Air Quality Standards, information on EPA's proposed revisions to the PM2.5 NAAQS, and the recent finding from the International Agency for Research on Cancer regarding the carcinogenicity of diesel exhaust.

We have also received one public comment to the AQMP that is relevant to the draft Appendix I, which I attach for your information. A member of the public also distributed a handout at a meeting of the AQMP Advisory Group relevant to the draft Appendix I, and the handout is also attached for your information. Prior to the October 11 meeting, we will be providing you another interim draft version of Appendix I, which will be prepared in conjunction with CARB. Additionally, we expect to have additional outside reviews of the draft Appendix by the end of this month. We will attach any additional comments relative to the draft Appendix as we receive them so that they will also be available to you prior to the October 11 meeting.
If any of you have additional comment on the draft Appendix I, please forward to me by the end of this month (Sept 30, 2012) if possible, but at the latest prior to the next meeting of the Advisory Council on October 11, 2012.

Revisions to the current draft made as a result of comments received by the end of September will be sent to you prior to the October 11 Advisory Council meeting for your review. Additionally, the revised draft will have all comments received as attachments.

Additional information regarding the Draft 2012 AQMP is available at http://www.aqmd.gov/aqmp/2012aqmp/index.htm.

Lastly, a reminder that the Advisory Council is subject to the California open meetings regulations. Please do not copy other Advisory Council members regarding any comments or correspondence. There will be opportunity for discussion at the meeting on October 11.

Thanks.

Jean Ospital
Health Effects Officer
South Coast Air Quality Management District
21865 Copley Drive
Diamond Bar, CA 91765
Phone: 909-396-2582
Fax: 909-396-3324
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REVIEW DRAFT
APPENDIX I

HEALTH EFFECTS

SEPTEMBER 2012

SOUTH COAST AIR QUALITY MANAGEMENT DISTRICT
GOVERNING BOARD

CHAIRMAN: WILLIAM A. BURKE, Ed.D.
Speaker of the Assembly Appointee

VICE CHAIR: DENNIS YATES
Mayor, Chino
Cities of San Bernardino

MEMBERS:

MICHAEL D. ANTONOVICH
Supervisor, Fifth District
County of Los Angeles

JOHN J. BENOIT
Supervisor, Fourth District
County of Riverside

MICHAEL A. CACCIOTTI
Mayor, South Pasadena
Cities of Los Angeles County/Eastern Region

JOSIE GONZALES
Supervisor, Fifth District
San Bernardino County Representative

RONALD O. LOVERIDGE
Mayor, City of Riverside
Cities Representative, Riverside County

JOSEPH K. LYOU, Ph.D.
Governor's Appointee

JUDITH MITCHELL
Councilmember, Rolling Hills Estates
Cities of Los Angeles County/Western Region

SHAWN NELSON
Supervisor, Fourth District
County of Orange

CLARK E. PARKER, Ph.D.
Senate Rules Appointee

JAN PERRY
Councilmember, Ninth District
City of Los Angeles

MIGUEL A. PULIDO
Mayor, Santa Ana
Cities of Orange County

EXECUTIVE OFFICER:

BARRY R. WALLERSTEIN, D.Env.

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Assistant Deputy Executive Officer
Planning, Rule Development, and Area Sources

Author

Jean Ospital, Dr PH
Health Effects Officer

Table of Contents

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 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 revisions. This document, which was prepared to satisfy that requirement, also includes the effects of the other major pollutants.

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 (morbidity) and increases in death rates (mortality).

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

- Increased mortality
- Increased health care utilization (hospitalization, physician and emergency room visits)
- Increased respiratory illness (symptoms, infections, and asthma exacerbation)
- Decreased lung function (breathing capacity)
- Lung inflammation
- Potential immunological changes
- Increased airway reactivity to a known chemical 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.

The evidence linking these effects to air pollutants is derived from population-based observational and field studies (epidemiological) as well as controlled laboratory studies involving human subjects and animals. There have been an increasing number of studies focusing on the mechanisms (that is, on learning how specific organs, cell types, and biochemicals 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 mostly pollutant-specific. This is appropriate, in that different pollutants usually 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, may sometimes act together to harm health more than they would acting separately. Nevertheless, as a practical matter, health scientists, as well as regulatory officials, usually must deal with one pollutant at a time in determining health effects and 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 toxic exposure 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 document.

This summary is drawn substantially from reviews presented previously (SCAQMD, 1996, 2003, 2007), and from reviews on the effects of air pollution by the American Thoracic Society (ATS, 1996), the U.S. EPA reviews for ozone (U.S. EPA, 2006), Carbon Monoxide (U.S. EPA, 2010), and Particulate Matter (U.S. EPA, 2004, 2009), from a published review of the health effects of air pollution (Brunekreef and Holgate, 2002), and from reviews prepared by the California EPA Office of the Environmental Health Hazard Assessment for Particulate Matter (Cal EPA, 2002) and for Ozone (Cal EPA, 2005). Additional materials are from EPA's current review of the ozone standard and health effects (EPA, 2011). More detailed citations and discussions on air pollution health effects can be found in these references.[1]

[1] Most of the studies referred to in this appendix are cited in the above sources. Only more recent specific references will be cited in this summary.

OZONE

Ozone is a highly reactive compound, and is 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, it can penetrate into the gas exchange region of the deep lung.

The EPA primary standard for ozone, adopted in 2008, is 0.075 ppm averaged over eight hours. The California Air Resources Board (CARB) has established standards of 0.09 ppm averaged over one hour and at 0.070 ppm averaged over eight hours.

The major subgroups of the population considered to be at increased risk from ozone exposure are outdoor exercising individuals, including children, and people with preexisting respiratory disease(s) such as asthma. The data base identifying the former group as being at increased risk to ozone exposure is much stronger and more quantitative than that for the latter group, probably because of a larger number of studies conducted with healthy individuals. The adverse effects reported with short-term ozone exposure are greater with increased activity because activity increases the breathing rate and the volume of air reaching the lungs, resulting in an increased amount of ozone reaching the lungs. Children may be a particularly vulnerable population to air pollution effects because they spend more time outdoors, are generally more active, and have a higher ventilation rate than adults.

A number of adverse health effects associated with ambient ozone levels have been identified from laboratory and epidemiological studies (EPA, 1996; 2006, 2011; ATS, 1996). These include increased respiratory symptoms, damage to cells of the respiratory tract, decrease in lung function, increased susceptibility to respiratory infection, and increased risk of hospitalization.

Increases in ozone levels are associated with elevated absences from school. The Children's Health Study, conducted by researchers at the University of Southern California, followed a cohort of children that live in 12 communities in Southern California with differing levels of air pollution for several years. A publication from this study reported that school absences in fourth graders for respiratory illnesses were associated with ambient ozone levels. An increase of 20 ppb ozone was associated with an 83% increase in illness-related absence rates (Gilliland, 2001).

The number of hospital admissions and emergency room visits for all respiratory causes (infections, respiratory failure, chronic bronchitis, etc.) including asthma

shows a consistent increase as ambient ozone levels increase in a community. These excess hospital admissions and emergency room visits are observed when hourly ozone concentrations are as low as 0.06 to 0.10 ppm.

Numerous recent studies have found positive associations between increases in ozone levels and excess risk of mortality. These associations persist even when other variables including season and levels of particulate matter are accounted for. This indicates that ozone mortality effects may be independent of other pollutants (Bell, 2004).

Multicity studies of short-term ozone exposures (days) and mortality have also examined regional differences. Evidence was provided that there were generally higher ozone-mortality risk estimates in northeastern U.S. cities, with the southwest and urban mid-west cities showing lower or no associations (Smith, 2009; Bell, 2008). Another long-term study of a national cohort found that long-term exposures to ozone were associated with respiratory-related causes of mortality, but not cardiovascular-related causes, when PM2.5 exposure were also included in the analysis.

Several population-based studies suggest that asthmatics are more adversely affected by ambient ozone levels, as evidenced by increased hospitalizations and emergency room visits. Laboratory studies have attempted to compare the degree of lung function change seen in age and gender-matched healthy individuals versus asthmatics and those with chronic obstructive pulmonary disease. While the degree of change evidenced did not differ significantly, that finding 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 degree of change may represent a substantially greater adverse effect overall.

Another publication from the Children's Health Study focused on children and outdoor exercise. In 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, 2002). These findings indicate that new cases of asthma in children are associated with heavy exercise in communities with high levels of ozone. While it has long been known that air pollution can exacerbate symptoms in individuals with respiratory disease, this is among the first studies that indicate ozone exposure may be causally linked to asthma onset.

In addition, human and animal studies involving both short-term (few hours) and long-term (months to years) exposures indicate a wide range of effects induced or associated with ambient ozone exposure. These are summarized in Table I-1.

TABLE I-1

Adverse Health Effects of Ozone (O3) - Summary of Key Studies

0_3 CONCENTRATION AND EXPOSURE HR., PPM	**HEALTH EFFECT**
Ambient air containing 0.10 - 0.15 daily 1-h max over days to weeks; ≥ 0.05 (8 hour average)	Decreased breathing capacity, in children, adolescents, and adults exposed to 0_3 outdoors Exacerbation of respiratory symptoms (e.g., cough, chest pain) in individuals with pre-existing disease (e.g., asthma) with low ambient exposure, decreased temperature, and other environmental factors resulting in increased summertime hospital admissions and emergency department visits for respiratory causes
≥0.12 (1-3h) ≥0.06 (6.6h) (chamber exposures)	Decrements in lung function (reduced ability to take a deep breath), increased respiratory symptoms (cough, shortness of breath, pain upon deep inspiration), increased airway responsiveness and increased airway inflammation in exercising adults Effects are similar in individuals with preexisting disease except for a greater increase in airway responsiveness for asthmatic and allergic subjects Older subjects (>50 yrs old) have smaller and less reproducible changes in lung function Attenuation of response with repeated exposure
≥0.12 with prolonged, repeated exposure (chamber exposures)	Changes in lung structure, function, elasticity, and biochemistry in laboratory animals that are indicative of airway irritation and inflammation with possible development of chronic lung disease Increased susceptibility to bacterial respiratory infections in laboratory animals

From: SCAQMD, 1996; EPA, 2007

Some lung function responses (volume and airway resistance changes) observed after a single exposure to ozone exhibit attenuation or a reduction in magnitude with repeated exposures. Although it has been argued that the observed shift in response is evidence of a probable adaptation phenomenon, it appears that while functional changes may exhibit adaptation, biochemical and cellular changes which may be

associated with episodic and chronic exposure effects may not exhibit similar adaptation. That is, internal damage to the respiratory system may continue with repeated ozone exposures, even if externally observable effects (chest symptoms and reduced lung function) disappear.

In a laboratory, exposure of human subjects to low levels of ozone causes reversible decrease 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. Similar lung volume changes have also been observed in adults and children under ambient exposure conditions (0.10 - 0.15 ppm). The responses reported are indicative of decreased breathing capacity and are reversible.

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 recently summarized (Brown, 2008). As shown in the figure below, there is an increasing response on lung function with increasing exposure levels in moderately exercising subjects.

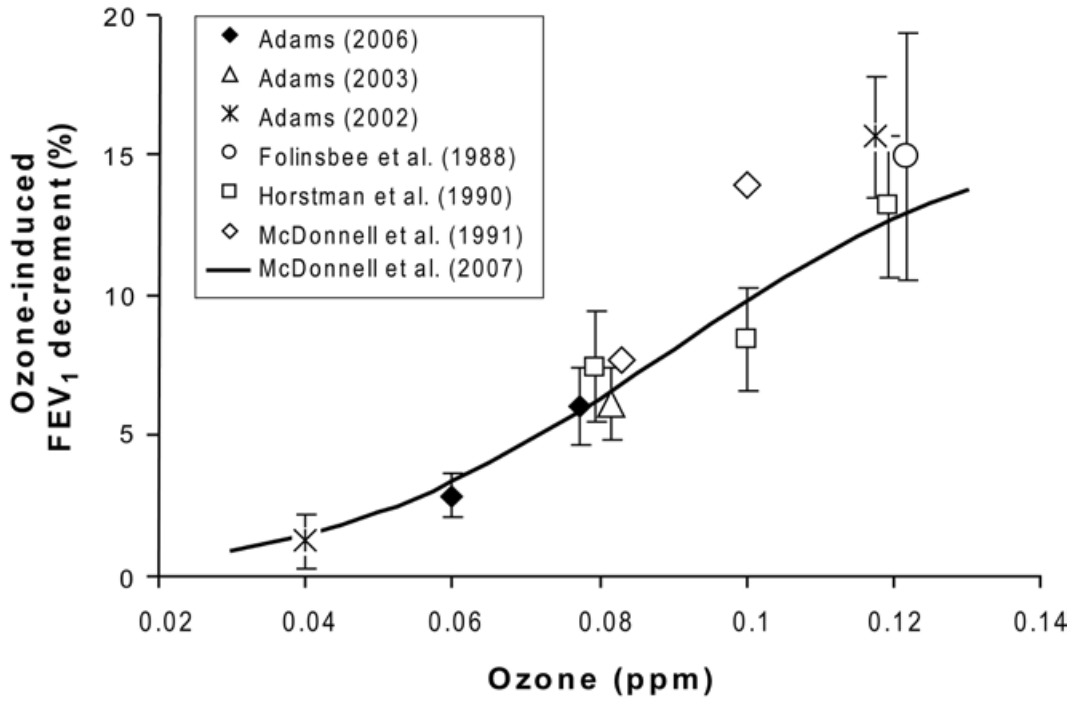

FIGURE I-1

Comparison of mean ozone-induced decrements in lung function following 6.6 hours of ozone exposure (from Brown, 2008)

In addition to controlled laboratory conditions, studies of individuals exercising outdoors, including children attending summer camp, have shown associations of reduced lung function with ozone exposure. There were wide ranges in responses among individuals.

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 (EPA, 2011).

In laboratory studies, cellular and biochemical changes associated with respiratory tract inflammation have also been consistently reported 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 cytokines and fibronectin. 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.

The susceptibility to ozone observed under ambient conditions could be due to the combination of pollutants that coexist in the atmosphere or ozone may actually sensitize these subgroups to the effects of other pollutants.

Some animal studies show results that indicate possible chronic effects including functional and structural changes of the lung. These changes indicate that repeated inflammation associated with ozone exposure over a lifetime may result in sufficient 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. An autopsy study involving Los Angeles County residents provided supportive evidence of lung tissue damage (structural changes) attributable to air pollution.

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 is 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. Confirmation by further studies is needed.

In summary, adverse effects associated with ozone exposures have been well documented, although the specific causal mechanism is still somewhat unclear.

It may be instructive to provide the overall EPA staff preliminary conclusions on the causality on ozone health effects for the health outcomes evaluated (EPA, 2011). These are provided in the two tables below.

TABLE I-2

Summary of Causal Determinations for Short-Term Exposures to Ozone

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

From EPA, 2011

TABLE I-3

Summary of Causal Determinations for Long-Term Exposures to Ozone

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

From EPA, 2011

PARTICULATE MATTER

Airborne particulates are a complex group of pollutants that vary in source, size and composition, depending on location and time. 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, may also be present.

Until several years ago, the health effects of particulates were focused on those sized 10 μm (micrometers) aerodynamic diameter and smaller. These can be inhaled through the upper airways and deposited in the lower airways and gas exchange tissues in the lung. These particles are referred to as PM10. EPA initially promulgated ambient air quality standards for PM10 of 150 $\mu g/m^3$ averaged over a 24-hour period, and 50 $\mu g/m^3$ for an annual average. EPA has since rescinded the annual PM10 standard, but kept the 24-hour standard.

In recent years additional focus has been placed on particles having an aerodynamic diameter of 2.5 μm or less (PM2.5). A greater faction of particles in this size range can penetrate and deposit deep in the lungs. The EPA recently lowered the air quality standards for PM2.5 to 35 $\mu g/m^3$ for a 24-hour average and reaffirmed 15 $\mu g/m^3$ 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 EPA promulgated the initial PM2.5 standards in 1997.

Since that time, numerous studies have been published, and some of the key studies were closely scrutinized and analyses repeated. The result is that there are now substantial data confirming the adverse health effects of PM2.5 exposures.

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 larger than 2.5 μm (often referred to as the coarse fraction) 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.

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 few years. These are generally referred to as "ultrafine" particles, with diameters of 0.1 μm or less. These particles are mainly from fresh emissions of combustion sources, but are also formed in the atmosphere from photochemical reactions. Ultrafine particles have relatively short half lives (minutes to hours) and rapidly grow through condensation and coagulation process into larger particles within the PM2.5 size range. These particles are garnering interest since laboratory studies indicate that their toxicity may be higher on a mass basis than larger particles, and there is evidence that these small particles can translocate from the lung to the blood and to other organs of the body.

There have been several reviews of the health effects of ambient particulate matter (ATS, 1996; Brunekreef, 2002; U.S. EPA, 2004; U.S. EPA, 2009). 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 (Cal EPA, 2002).

The major types of effects associated with particulate matter include:

- Increased mortality
- Exacerbation of respiratory disease and of cardiovascular disease as evidenced by increases in:
  - -Respiratory symptoms
  - -Hospital admissions and emergency room visits
  - -Physician office visits
  - -School absences
  - -Work loss days
- Effects on lung function
- Changes in lung morphology

The current federal and California standards are listed below:

TABLE I-4

Ambient Air Quality Standards for Particulate Matter

STANDARD	FEDERAL	CALIFORNIA
PM10 24-Hour average	150 μg/m^3	50 μg/m^3
PM10 Annual Average	--	20 μg/m^3
PM 2.5 24-Hour Average	35 μg/m^3	--
PM 2.5 Annual Average	15 μg/m^3	12 μg/m^3

Short-Term Exposure Effects

Epidemiological studies have provided evidence for most of the effects listed above. An association between increased daily or several-day-average concentrations of PM10 and excess mortality and morbidity is consistently reported from studies involving communities across the U.S. as well as in Europe, Asia, and South America. A review and analysis of epidemiological literature for acute adverse effects of particulate matter was published by the American Thoracic Society in 1996. Several adverse effects were listed as associated with daily PM10 exposures, as listed in Table I-5.~~undertaken by Dockery and Pope to estimate these effects as percent increase in mortality associated with each incremental increase of PM10 by 10 μg/m^3. The estimates are presented in Table I-5.~~ It also appears that individuals who are elderly or have preexistent lung or heart disease are more susceptible than others to the adverse effects of PM10 (ATS, 1996). Since then m~~M~~any more recent studies have confirmed that excess mortality and morbidity are associated with short term particulate matter levels (Pope, 2006).

Estimates of mortality effects from ~~these~~ studies of PM10 exposures range from 0.3 to 1.7% increase for a 10 μg/m^3 increase in PM10 levels. The National Morbidity, Mortality, and Air Pollution Study (NMMAPS), a study of 20 of the largest U.S. cities, determined a combined risk estimate of about a 0.5% increase in total mortality for a 10 μg/m^3 increase in PM10 (Samet, 2000a). This study also analyzed the effects of gaseous co-pollutants. The results indicated that the association of PM10 and mortality were not confounded by the presence of the gaseous pollutants. When the gaseous pollutants were included in the analyses, the significance of the PM10 estimates remained. The PM10 effects were reduced somewhat when O_3 was also considered and tended to be variably decreased when NO_2, CO, and SO_2 were

added to the analysis. These results argue that the effects are likely due to the particulate exposures; they cannot readily be explained by coexisting weather stresses or other pollutants.

An expansion of the NMMAPS study to 90 U.S. Cities also reported association with PM10 levels and mortality (Samet 2000b). It was discovered that this study was one that used a flawed statistical software package. The investigators have reanalyzed the data using corrected settings for the software (Dominici, 2002a, Dominici 2002b). When the estimates for the 90 cities in the study were recalculated, the estimate changed from 0.41% increase in mortality for a 10 $\mu g/m^3$ increase in PM10 to a 0.27% increase. There remained a strong positive association between acute exposure to PM10 and mortality. Thus while the quantitative estimate was reduced, the major findings of the study did not change.

TABLE I-5

Combined Effect Estimates of Daily Mean Particulate Pollution (PM10)

	% CHANGE IN HEALTH INDICATOR PER EACH 10 $\mu g/m^3$ 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

TABLE I-5 (concluded)

Combined Effect Estimates of Daily Mean Particulate Pollution

	% CHANGE IN HEALTH INDICATOR PER EACH 10 μg/m^3 INCREASE IN PM10
Cough	2.5
Decrease in Lung Function	
Forced expiratory volume	0.15
Peak expiratory flow	0.08

* One study only

(Source: American Journal of Respiratory and Critical Care Medicine, Vol. 153, 113-50, 1996)

Studies of PM2.5 also find associations with elevated mortality. The estimates for PM2.5 generally are in the range of 2.0 to 8.5% increase in total deaths per 25 μg/m^3 increase in 24-hour PM2.5 levels. The estimates for cardiovascular related mortality range from 3.0 to 7.0% per 25 μg/m^3 24-hour PM2.5, and for respiratory mortality estimates range from 2.0 to 7.0% per 25 μg/m^3 24-hour PM2.5.

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. Other studies in Mexico City and Santiago, Chile reported that PM10-2.5 was as important as PM2.5. Overall effects estimates for PM10-2.5 fall in the range of 0.5 to 6.0 % excess mortality per 25 μg/m^3 24-hour average.

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. More research is needed to better assess the relative effects of fine (PM2.5) and coarse (PM10-2.5) fractions of particulate matter on mortality.

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 effects estimates are generally higher than the effects for mortality. The effects are associated with measures of PM10 and PM2.5. Effects are also associated with PM10-2.5. Thus, it appears that when a relatively small number of people experience severe effects, larger numbers experience milder effects, which may relate either to the coarse or to the fine fraction of airborne particulate matter.

In the NMMAPS study, hospital admissions for those 65 years or older were assessed in 14 cities. Hospital admissions for these individuals showed an increase of 6% for cardiovascular diseases and a 10% increase for respiratory disease admissions, per 50 $\mu g/m^3$ increase in PM10. The excess risk for cardiovascular disease ranges from 3-10% per 50 $\mu g/m^3$ PM10 and from 4-10% per 25 $\mu g/m^3$ PM2.5 or PM10-2.5.

Similarly, school absences, lost workdays and restricted activity days have also been used in some studies as indirect indicators of acute respiratory conditions. The results are suggestive of both immediate and delayed impact on these parameters following elevated particulate matter exposures. These observations are consistent with the hypothesis that increased susceptibility to infection follows particulate matter exposures.

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 3% to 42% for medical visits for respiratory illnesses was found corresponding to a 50 $\mu g/m^3$ change in PM10. A limited 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.

The biological mechanisms by which particulate matter can produce health effects are being investigated in laboratory studies. Inflammatory responses in the respiratory system in humans and animals exposed to concentrated ambient particles have been measured. These include effects such as increases in neutrophils in the lungs. Other changes reported include increased release of cytokines and interleukins,

chemicals released as part of the inflammatory process. The effects of particulate matter may be mediated in part through the production of reactive oxygen species during the inflammatory process. Recent reviews discuss mechanistic studies in more detail (Brunekreef, 2002; Brook, 2004).

Long-Term Exposure Effects

While most studies have evaluated the acute effects, some studies specifically focused on evaluating the effects of chronic exposure to PM10 and PM2.5. Studies have analyzed the mortality of adults living in different U.S. cities. After adjusting for important risk factors, taken as a whole these studies found a positive association of deaths and exposure to particulate matter. A similar association was observable in both total number of deaths and deaths due to specific causes. The largest effects were observed from cardiovascular causes and ischemic heart disease. A shortening of lifespan was also reported in these studies.

Since the initial promulgation by EPA of the National Ambient Air Quality Standards for PM2.5, controversy has remained over the association of mortality and exposures to PM2.5. Thus an expanded discussion of these studies is presented below.

Significant associations for PM2.5 for both total mortality and cardiorespiratory mortality were reported in a study following a national cohort recruited by the American Cancer Society for a Cancer Preventions Study over several years. A re-analysis of the data from this study confirmed the initial finding (Krewski, 2000). In this study, mortality rates and PM2.5 levels were analyzed for 51 metropolitan areas of the U.S. Average levels from monitors in each area were used to estimate exposures. At these levels of aggregation, regional differences in the association of PM2.5 and mortality were noted, with higher associations in the Northeast, and lower or non-significant associations in the West.

The Harvard Six Cities Study evaluated several size ranges of particulate matter and reported significant associations with PM15, PM2.5, sulfates, and non-sulfate particles, but not with coarse particles (PM15 – PM2.5). An extension of the Harvard Six Cities Cohort confirmed the association of mortality with PM2.5 levels (Laden, 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 compounds. An update to this study covering a follow-up over the years 1974 to 2009 (Lepeule, 2012) was recently published. 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.

A 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 ug/m3 increase in fine particulates was associated with approximately a 4% increase in total mortality, a 6% increase in cardiopulmonary mortality, and an 8% increase risk of lung cancer mortality (Pope, 2002). The magnitude of effects is larger in the long-term studies than in the short-term investigations. In an additional re analysis and extension of the American Cancer Society cohort from 1982 to 2000 (Krewski, 2009), and including additional metropolitan areas for the most recent years, effects estimates on mortality were similar, though somewhat higher, than those reported previously.

Other national studies include an analysis of mortality and PM2.5 exposures in a Medicare population. Zeger and Associates (2008) assembled a Medicare cohort by including all Medicare enrollees residing in zip codes with centroids within 6 miles of a PM2.5 monitor. PM2.5 data was obtained from the monitoring stations, and mean annual levels were called for the zip codes within six miles of each monitor. The estimated associations between exposures to PM2.5 and mortality for the eastern and central portions of the U.S were similar to those previously published in the Six Cities Study and the American Cancer Society cohorts. The authors reported that there were no significant associations between zip code levels of PM2.5 and mortality rates in the western region of the U.S. This lack of association 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 these counties. The authors further reported that they found no associations of PM2.5 with mortality in persons aged 85 years or higher.

Analyses of mortality and PM2.5 levels specific to California have also been reported. A cohort of elderly individuals (average age of 65 yr in 1973) recruited from 11 California counties was followed over several years (Enstrom, 2005). An association for exposure with all cause deaths was reported from 1973–1982. However, no significant association was found in the later time period of 1983–2002. Pollutant levels were taken from ambient monitors and averaged over each county to estimate exposures.

Two analyses of the American Cancer Society cohort 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. Using data from monitoring stations in the Los Angeles area, one study applied interpolation methods (Jerrett, 2005) and another applied land use regression techniques (Krewski, 2009) to estimate exposures to the study individuals. Significant associations of PM2.5 with mortality from all causes and cardiopulmonary disease were reported, with the magnitude of risks being up to five times higher than those from the national studies of the American Cancer Society cohort. This provides evidence that using methods to provide more detailed exposure estimates can result in stronger associations of PM2.5 and mortality.

Two recent reports have been released looking at air pollution and health effects in California. One study (Lipsett, 2011) followed school teachers recruited in 1995, and followed through 2005. Pollutant exposures at the subject residence were estimated using data from ambient monitors, and extrapolated using a distance weighted method. The authors reported significant association of PM2.5 levels and mortality from ischemic heart disease, but no associations were found with all cause, cardiovascular, or respiratory disease.

The second study (Jerrett, 2011) followed individuals in ~~the Los Angeles area~~ California from the American Cancer Society cohort recruited starting in 1982, with follow up to 2000. Pollutant levels at subject residences were estimated using several methods. All but one of the methods found no association of all-cause mortality with PM2.5 levels. All exposure estimation methods were reported to have found significant associations with ischemic heart disease mortality, however. The authors noted that mortality rates differ in urban areas compared to non-urban areas, and so included a variable for this in a land use regression model to estimate effects on mortality. When the authors applied the land use regression model including an urban indicator to estimate exposures, all-cause mortality, mortality from cardiovascular disease, and mortality from ischemic heart disease were all significantly associated with PM2.5 levels.

The U.S. EPA has recently proposed to lower the annual National Ambient Air Quality Standard for PM2.5 (U.S. EPA, 2012a). EPA also released a Regulatory Impact Analysis (U.S. EPA 2012b)which looked at the costs and benefits of alternate PM2.5 stand levels. As part of the analysis, EPA also looked at California specific studies regarding PM2.5 and mortality published in the scientific literature. The 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 cohort studies conducted in California indicate higher risks than the risk estimates we applied." Thus in EPAs judgment the California related studies provided estimates of mortality consistent with or higher than those from the national studies.

Other studies report evidence indicating that particulate matter exposure early in pregnancy may be associated with lowered birth weights (Bobak, 1999). Studies from the U.S., the Czech Republic and Mexico City have reported that neonatal and early postnatal exposure to particulate matter may lead to increased infant mortality. A more recent study in Southern California found increased risks for infant deaths associated with exposures to particulates and other pollutants (Ritz, 2006). These results suggest that infants may be a subgroup affected by particulate matter exposures.

In addition, some long-term effect studies have reported an increased risk of mortality from lung cancer associated with particulate matter exposures. A study involving California Seventh Day Adventists (very few of whom smoke) has reported an association of lung cancer mortality with PM10 levels. It is not clear from these studies whether the association relates to causation of disease, or whether individuals with cancer are more susceptible to other effects of particles leading to the observed mortality association. A study that followed a large number of individuals living in the largest U.S. cities found elevated lung cancer risk associated with long-term average PM2.5 levels (Pope, 2002).

Several studies have assessed the effects of long-term particulate matter exposure on respiratory symptoms and lung function changes. Associations have been found with symptoms of chronic bronchitis and decreased lung function. A study of school children in 12 communities in Southern California showed significant association of particulate matter with bronchitis or phlegm in children with asthma. These effects were also associated with NO_2 and acid vapor levels.

A cohort of fourth graders from the Southern California communities was followed over a period of four years by the Children's Health Study. A lower rate of growth in lung function was found in children living in areas with higher levels of particulate pollution (Gauderman, 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, 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 regain some of the lung function growth rate (Avol, 2001). By the time the fourth graders graduated from high school, a significant number showed lower lung function. The risk of lower lung function was about five times higher in children with the highest PM2.5 exposure when compared to the lowest exposure communities (Gauderman, 2004). These deficits are likely to persist since the children were at the end of their growth period.

Despite data gaps, the extensive body of epidemiological studies has both qualitative and quantitative consistency suggestive of causality. A considerable body of evidence from these studies suggests that ambient particulate matter, alone or in combination with other coexisting pollutants, is associated with significant increases in mortality and morbidity in a community.

In summary, the scientific literature indicates that an increased risk of mortality and morbidity is associated with particulate matter at ambient levels. 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.

EPA staff has presented conclusions on causal determination of several health effects based on a recent review of the available scientific studies (EPA, 2009). These are depicted in the Table below.

TABLE I-6

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

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

From EPA, 2009

ULTRAFINE PARTICLES

As noted above, numerous studies have found association of particulate matter levels with adverse effects, including mortality, hospital admissions, and respiratory disease symptoms. The vast majority of these studies used particle mass of PM10 or PM2.5 as the measure of exposure. Some researchers have postulated, however, that ultrafine particles may be responsible for some of the observed associations of particulate matter and health outcomes (Oberdorster, et al, 1995; Seaton, et al, 1995). Ultrafine particles are generally classified of 0.1 μm and small diameter.

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

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

Smaller particles can also be inhaled deep into the lungs. As much as 50% of 0.02 µm diameter particles are estimated to be deposited in the alveolar region of the lung. There is complex nature of the relation between deposition and particle size. The ultrafine particles generally have higher fractional deposition in the alveolar region. However, for the smaller nucleation mode (particles less than 0.01 µm size) the deposition in the alveolar region declines, but increases in the extrathoracic region.

Exposures of laboratory animals to ultrafine particles have found cardiovascular and respiratory effects. Mice exposed to concentrated near roadway ultrafine particles showed larger early atherosclerotic lesions than mice exposed to PM2.5 or filtered air (Arujo, 2008). In a mouse allergy model, exposures to concentrated ultrafine particles resulted in a greater response to antigen challenge to ovalbumin (Li, 2010), indicating that vehicular traffic exposure could exacerbate allergic inflammation in already-sensitized animals.

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, 2011, for example found exposure to diesel exhaust particulate attenuated both acetylcholine and sodium-nitroprusside -induced vasorelaxation.

There are no long-term studies of human population exposure to ultrafine particle, as there is a lack of a monitoring network in the U.S. There have been several cross sectional epidemiological studies of ultrafine particles, mainly from Europe. Some of these studies found effects on hospital admissions, emergency department visits, for respiratory and cardiovascular effects. Other studies, however, have not found such effects (EPA, 2009). Concentrations of ultrafine particles can vary geographically, and it is not clear how well central site monitors may capture actual exposures.

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 (EPA, 2009). These are depicted in the table below.

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

TABLE I-7

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

SHORT-TERM EXPOSURES	
Health Outcome	**Causality Determination**
Cardiovascular effects	Suggestive
Respiratory effects	Suggestive
Central nervous system	Inadequate information to assess
Mortality	Inadequate
LONG-TERM EXPOSURES	
Health Outcome	**Causality Determination**
Cardiovascular effects	Inadequate
Respiratory effects	Inadequate
Mortality	Inadequate
Reproductive and developmental	Inadequate
Cancer, Mutagenicity, Genotoxicity	Inadequate

From EPA, 2009

CARBON MONOXIDE

The high affinity of carbon monoxide (CO) to bond with oxygen-carrying proteins (hemoglobin and myoglobin) results in reduced oxygen supply in the bloodstream of exposed individuals. The reduced oxygen supply 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 (U.S. EPA, 2000, 2010).

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). Exposure to CO is often evaluated in terms of COHb levels in blood measured as percentage of total hemoglobin bound to CO. COHb levels in non-smokers range between 0.3 and 0.7% and 5 to 10% in smokers. COHb levels in excess of 1.5% in a significant proportion of urban non-smoking populations can be considered as evidence of widespread exposure to environmental CO.

Under controlled laboratory conditions, healthy subjects exposed to CO sufficient to result in 5% COHb levels exhibited reduced duration of maximal exercise performance and consumption of oxygen. Studies involving subjects with coronary artery disease who engaged in exercise during CO exposures have shown that COHb levels as low as 2.4% can lead to earlier onset of electrocardiograph changes indicative of deficiency of oxygen supply to the heart. Other effects include an earlier onset of chest pain, an increase in the duration of chest pain, and a decrease in oxygen consumption.

Findings of epidemiologic studies have observed associations between ambient CO concentration and emergency department visits and hospital emissions for ischemic heart disease and other cardiovascular diseases.

Animal studies associated with long-term exposure to CO resulting in COHb levels that are equivalent to those observed in smokers have shown indication of reduction in birth weight and impaired neurobehavior in the offspring of exposed animals.

Epidemiological studies conducted in Southern California have indicated an association with CO exposure during pregnancy to increases in pre-term births. (Ritz, 2000). However, the results were not consistent in different areas studied. The increase in the pre-term births was also associated with PM10 levels. Another study found increased risks for cardiac related birth defects with carbon monoxide exposure in the second month of pregnancy (Ritz, 2002). Toxicological studies in laboratory animals with higher than ambient levels of CO have also reported decrements in birth weight and prenatal growth.

EPA staff has presented conclusions on causal determination of the health effects of carbon monoxide based on a recent review of the available scientific studies (EPA, 2010). These are depicted in the table below.

TABLE I-8

Causal Determination for Health Effects of Carbon Monoxide

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

From EPA, 2010

NITROGEN DIOXIDE

The U.S. EPA has recently reviewed the health effects of nitrogen dioxide (U.S. EPA, 2008a). Evidence for low-level nitrogen dioxide (NO_2) exposure effects is derived from laboratory studies of asthmatics and from epidemiological studies. Additional supportive evidence is derived from animal studies.

Epidemiological studies using the presence of an unvented gas stove as a surrogate for indoor NO_2 exposures suggest an increased incidence of respiratory infections or symptoms in children.

Recent studies related to outdoor exposure have found health effects associated with ambient NO_2 levels, including respiratory symptoms, respiratory illness, decreased lung function, increased emergency room visits for asthma, and cardiopulmonary mortality. However, since NO_2 exposure generally occurs in the presence of other pollutants, such as particulate matter, these studies are often unable to determine the specific role of NO_2 in causing effects.

The Children's Health Study in Southern California found associations of air pollution, including NO_2, PM10, and PM2.5, with respiratory symptoms in asthmatics (McConnell, 1999). Particles and NO_2 were correlated, and effects of individual pollutants could not be discerned. A subsequent analysis indicated a stronger role for NO2 (McConnell, 2002).

Ambient levels of NO_2 were also associated with a decrease in lung function growth in a group of children followed for eight years. In addition to NO_2, the decreased growth was also associated with particulate matter and airborne acids. The study authors postulated that these may be a measure of a package of pollutants from traffic sources. (Gauderman, 2004).

Results from controlled exposure studies of asthmatics demonstrate an increase in the tendency of airways to contract in response to a chemical stimulus (bronchial reactivity). Effects were observed with exposures from 0.1 to 0.3 ppm NO_2 for periods ranging from 30 minutes to 3 hours. A similar response is reported in some studies with healthy subjects at higher levels of exposure (1.5 - 2.0 ppm). Mixed results have been reported when people with chronic obstructive lung disease are exposed to low levels of NO_2.

Short-term controlled studies of animals exposed to NO_2 over a period of several hours indicate cellular changes associated with allergic and inflammatory response and interference with detoxification processes in the liver. In some animal studies

the severity of the lung structural damage observed after relatively high levels of short-term ozone exposure is observed to increase when animals are exposed to a combination of ozone and NO_2.

In animals, longer-term (3-6 months) repeated exposures at 0.25 ppm appear to decrease one of the essential cell-types (T-cells) of the immune system. Non-specific changes in cells involved in maintaining immune functions (cytotoxic T-cells and natural killer cells) have been observed in humans after repeated exposure (4-6 days) to >0.6 ppm of NO_2 (20 min. - 2 hours). All these changes collectively support the observation reported both in population and animal studies of increased susceptibility to infections, as a result of NO_2 exposure.

The U.S. EPA recently adopted a new short-term standard of 100 ppb (0.1 ppm) averaged over 1 hour. The standard was designed to protect against increases in airway reactivity in individuals with asthma observed in controlled exposure studies, as well as respiratory symptoms observed in epidemiological studies.

SULFUR DIOXIDE

Controlled laboratory studies involving human volunteers have clearly identified asthmatics as the most 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 significant alteration of lung function, such as increases in airway resistance and decreases in breathing capacity. In some, the exposure can result in severe symptoms necessitating the use of medication for relief. The response to SO_2 inhalation is observable within 2 minutes of exposure, increases further with continuing exposure up to 5 minutes then remains relatively steady as exposure continues. SO_2 exposure is generally not associated with any delayed reactions or repetitive asthmatic attacks.

In epidemiologic studies, associations of SO_2 levels with increases in respiratory symptoms, increases in emergency department visits and hospital admissions for respiratory-related causes have been reported.

The U.S. EPA has recently revised the SO_2 air quality standard. The previous 24-hour standard was rescinded and replaced with a new 1-hour standard at 75 ppb (0.075 ppm) to protect against high short-term exposures.

Animal studies have shown that despite SO_2 being a respiratory irritant, it does not cause substantial acute or chronic toxicity in animals exposed at ambient concentrations. However, relatively high exposures (10 ppm of SO_2 for 72 hours) in mice can lead to tissue damage, fluid accumulation and sloughing of respiratory lining. Sensitization to allergies is observable in guinea pigs repeatedly exposed to high levels (72 ppm) of SO_2. This effect needs further evaluation in clinical and population studies to identify any chronic exposure impact on both asthmatic incidence and attacks in a population.

Some epidemiological studies indicate that the mortality and morbidity effects associated with the fine fraction of particles show a similar association with ambient SO_2 levels. In these studies, efforts to separate the effects of SO_2 from fine particles have not been successful. Thus, it is not clear whether the two pollutants act synergistically, or whether being generated from similar combustion sources, they represent the same pollution index for the observed effects.

SULFATES

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.

In recent years, a vast majority of effects (mortality and morbidity) associated with fine particles (PM2.5) and sulfur dioxide have shown a similar association with ambient sulfate levels in some population studies. The efforts to fully separate the effects of sulfates from other coexisting pollutants have not been successful. This may be due to the fact that these pollutants covary under ambient conditions, having been emitted from common sources; and the effects observed may be due to the combination of pollutants, rather than a single pollutant.

A clinical study involving exposure of human subjects to sulfuric acid aerosol indicated that adolescent asthmatics may be a susceptible population subgroup with some changes in lung function observed with exposures below 100 $\mu g/m^3$. In general, however, laboratory exposures of human volunteers to sulfates at or near ambient levels have not found significant changes in lung function.

Results from animal studies involving exposures to sulfuric acid aerosol, ammonium bisulfate and ammonium sulfate indicate that acidic particles (former two) are more toxic than non-acidic particles (latter). In addition, the severity or magnitude of both

mortality and morbidity effects is relatively higher in population studies of the eastern United States and Canada where sulfate concentrations are higher than for those observed in the western United States. Mixed results have been reported from studies which attempted to ascertain the role of acidity in determining the observed toxicity.

LEAD

The U.S. EPA has recently reviewed the health effects of ambient lead exposures in conjunction with a review of the NAAQS for lead. (U.S. EPA 2006b; U.S. EPA 2007b). The following summary is taken from these reviews.

There are a number of potential public health effects at low level exposures. The health implications are generally indexed by blood lead levels, which are related to lead exposures both from inhalation as well as from ingestion. As identified by EPA, effects includeimpacts on population IQ, as well as heart disease and kidney disease. The array of health effects includes the following.

- Heme biosynthesis and related functions;
- Neurological development and function;
- Reproduction and physical development;
- Kidney function;
- Cardiovascular function
- Immune function

Children appear to be sensitive to the neurological toxicity of lead, with effects observed at blood lead concentration ranges of 5 – 10 µg/dL, or possibly lower. No clear threshold has yet been established for such effects.

According to the 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.

EPA has recently revised the NAAQS for lead to a level of 0.15 µg/m^3 averaged over a 3 month period to protect against lead toxicity. The following two charts, taken from the U.S. EPA review, depict the health effects of lead in relation to blood levels.

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

FIGURE I-2

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

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				

FIGURE I-3

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

TOXIC AIR CONTAMINANTS

Toxic air contaminants are pollutants for which there generally are no ambient air quality standards. Under California's Air Toxics Program, CARB staff and Office of Environmental Health Hazard Assessment (OEHHA) assess the health effects of substances that may pose a risk of adverse health effects. These effects are usually an increased risk for cancer or adverse birth outcome. 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.

CARB and OEHHA also establish 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.

The District conducted studies on the ambient concentrations and estimated the potential health risks from air toxics (SCAQMD, 2008). In the latest study, a two year monitoring program was undertaken at 10 sites throughout the SCAB over the time period 2004-2006. Over 30 substances were measured, and annual average levels were calculated. The results showed that the overall risk for excess cancer from a 70-year lifetime exposure to the levels of air toxics calculated as the average level at the 10 sites was about 1,200 in a million. The largest contributor to this risk was diesel ~~exhaust~~particulate matter, accounting for about 84% of the air toxics risk. A breakdown of the major contributors to the air toxics risk is shown in ~~FIGURE I-2~~FIGURE I-4.

While the California Air Resources Board listed Diesel Particulate Matter as a Toxic Air Contaminant in 1989, the International Agency for Research on Cancer, an arm of the World Health Organization, recently convened an international panel of scientists to review the published literature regarding the carcinogenicity of diesel combustion emissions. The panel concluded that Diesel Exhaust is a substance that causes cancer in humans (Benbrahim-Tallaa, 2012).

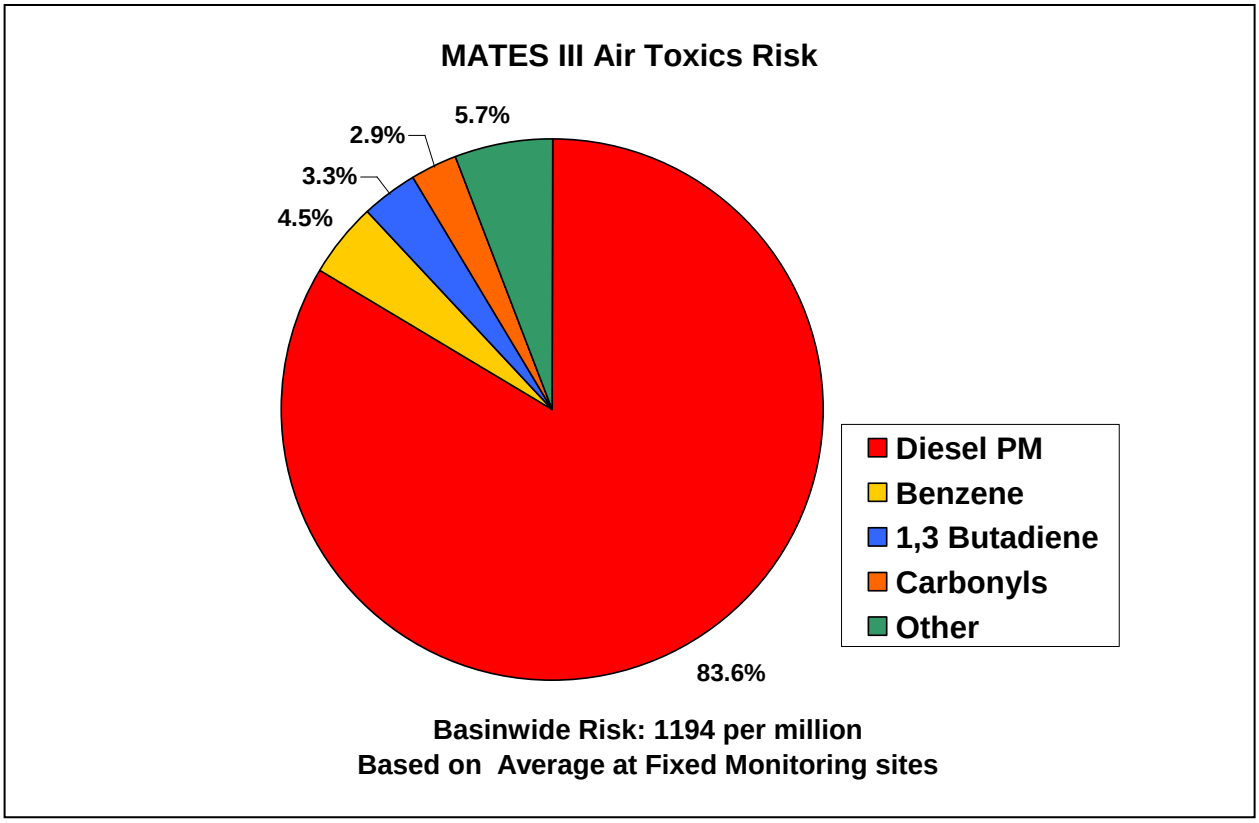

FIGURE I-4~~2~~

Major Pollutants Contributing to Air Toxics Cancer Risk in the South Coast Air Basin

For non-cancer health effects, OEHHA has developed acute and chronic Reference Exposure Levels (RELs). RELs are concentrations in the air below which adverse health effects are not likely to occur. Acute RELs refer to short-term exposures, generally of one-hour duration. Chronic RELs refer to long-term exposures of several years. 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. The measured levels from the most recent study were below the applicable Reference Exposure Levels.

The key air toxics contributing to risk from mobile and stationary sources are listed in TABLE I-9.

TABLE I-9

Key Toxic Air Contaminants in the SCAB

MOBILE SOURCES	STATIONARY SOURCES
Acetaldehyde	Hexavalent Chromium
Benzene	Methylene Chloride
1,3 Butadiene	Nickel
Diesel ~~Exhaust~~Particulate Matter	Perchloroethylene
Formaldehyde	Trichloroethylene

CONCLUSION

A large body of scientific evidence shows that the adverse impacts of air pollution in 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, earlier mortality ~~and air pollution~~.

As the scientific methods for the study of air pollution health effects has progressed over the past decades, adverse effects have been shown to occur at lower levels of exposure. For some pollutants, no clear thresholds for effects have been demonstrated. The new findings have, in turn, led to the revision and lowering of National Ambient Air Quality Standards which, in the judgment of the Administrator of the U.S. EPA, are necessary to protect public health. The figures below are meant to convey some of the historical context to recent revisions to the NAAQS for ozone and for particulate matter.

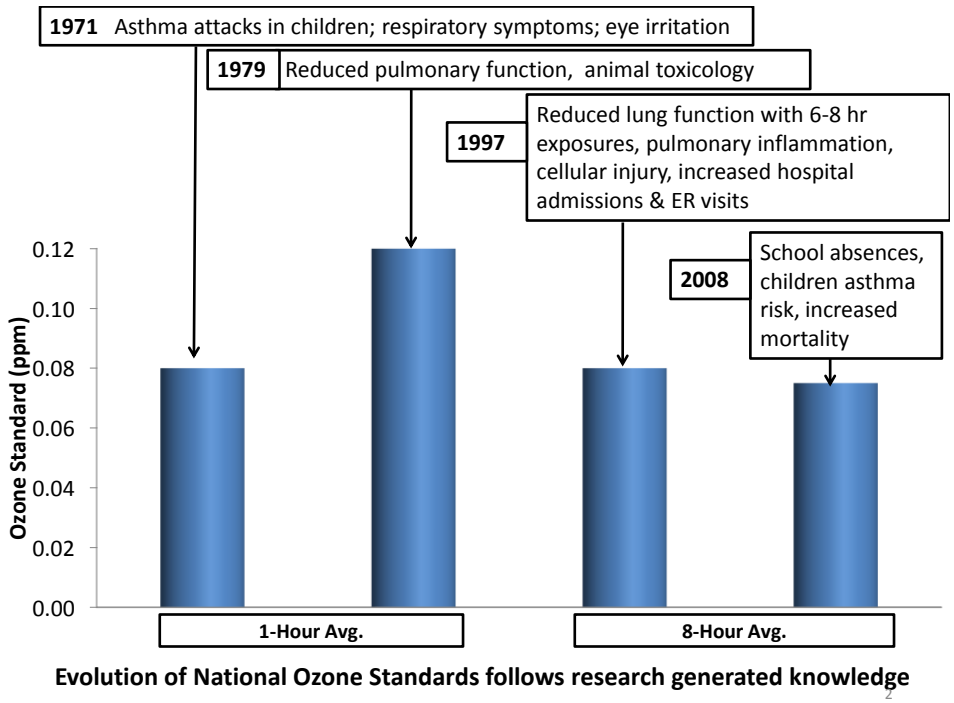

FIGURE I-4

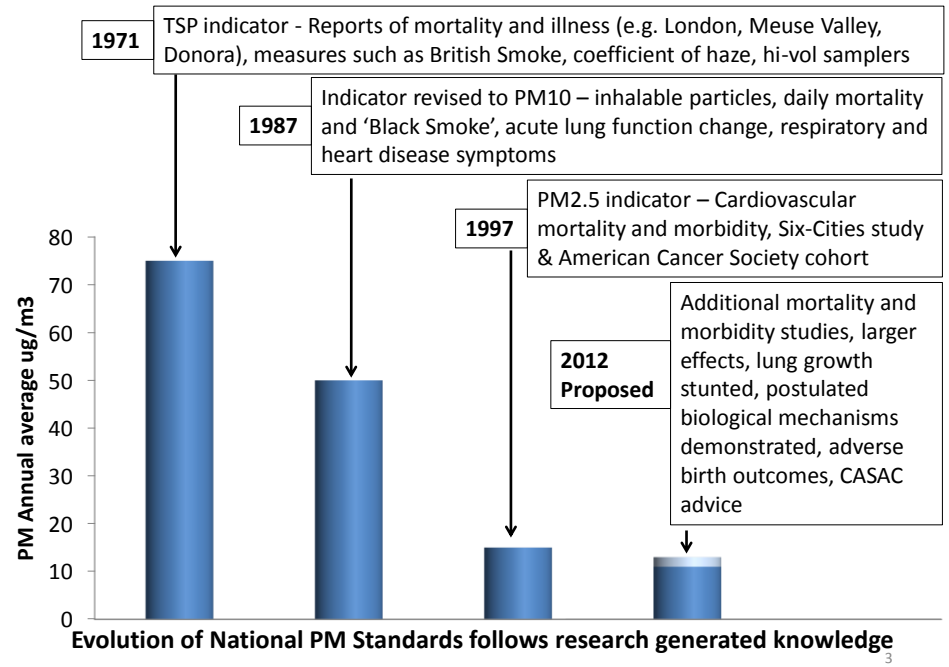

FIGURE I- 5

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OEHHA Comments on 2012 Appendix I-Health Effects

From: Marty, Melanie@OEHHA [mailto:Melanie.Marty@oehha.ca.gov]
Sent: Monday, October 01, 2012 4:25 PM
To: Jean Ospital
Subject: FW: Review of Draft 2012 AQMP Appendix I

Hi Jean – Bart and staff reviewed the report and have comments embedded in the pdf. They note that there are many more recent studies that are not cited. May be worth adding more, particularly where they note in the comments.

Hope this is helpful,

Melanie

Melanie Marty, Ph.D.
Assistant Deputy Director
Scientific Affairs Division
Office of Environmental Health Hazard Assessment
(916) 323-8808

From: Ostro, Bart@OEHHA
Sent: Monday, October 01, 2012 3:49 PM
To: Marty, Melanie@OEHHA
Subject: RE: Review of Draft 2012 AQMP Appendix I

Here it is. My general assessment is that for Pm and ozone many of the refs are old and a lot of new studies (2005 on) are not included...I'm not sure how much time Jean wants to put into this. We made some suggested refs along the way but there are dozens more that could be included in an a more current review. b

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From: Marty, Melanie@OEHHA
Sent: Monday, October 01, 2012 12:29 PM
To: Ostro, Bart@OEHHA
Subject: FW: Review of Draft 2012 AQMP Appendix I

Hi Bart – Did you guys ever generate comments on the SCAQMD draft?

M.

Melanie Marty, Ph.D.
Assistant Deputy Director
Scientific Affairs Division
Office of Environmental Health Hazard Assessment
(916) 323-8808

From: Jean Ospital [mailto:JOspital@aqmd.gov]
Sent: Tuesday, September 18, 2012 9:57 AM
To: Marty, Melanie@OEHHA
Cc: Elaine Chang; Philip Fine; Barbara Baird; William Wong
Subject: Review of Draft 2012 AQMP Appendix I

Melanie,

Thank you for your willingness to provide a review of the Draft Appendix I of the District's 2012 Air Quality Management Plan.

As background, the California Health and Safety Code Section 40471 calls for the District to prepare a report on the health impacts of particulate matter pollution in the South Coast Air Basin as part of the preparation of air quality management plans. Appendix I of the AQMP is a review of air pollution health effects, with the section dealing with particulate matter intended to fulfill this requirement. The current draft is available at the following link. http://www.aqmd.gov/aqmp/2012aqmp/draft/Appendices/AppxI.pdf. Additional materials related to the AQMP are available at http://www.aqmd.gov/aqmp/2012aqmp/index.htm.

As we discussed today, receiving the review before the end of this month would be most helpful for us.

Please give me a call if I can provide any additional information.

Best regards,

Jean

****

Jean Ospital
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REVIEW DRAFT
APPENDIX I

HEALTH EFFECTS

SEPTEMBER 2012

SOUTH COAST AIR QUALITY MANAGEMENT DISTRICT
GOVERNING BOARD

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BARRY R. WALLERSTEIN, D.Env.

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Jean Ospital, Dr PH
Health Effects Officer

Table of Contents

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 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 revisions. This document, which was prepared to satisfy that requirement, also includes the effects of the other major pollutants.

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 (morbidity) and increases in death rates (mortality).

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

- Increased mortality
- Increased health care utilization (hospitalization, physician and emergency room visits)
- Increased respiratory illness (symptoms, infections, and asthma exacerbation)
- Decreased lung function (breathing capacity)
- Lung inflammation
- Potential immunological changes
- Increased airway reactivity to a known chemical 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

The evidence linking these effects to air pollutants is derived from population-based observational and field studies (epidemiological) as well as controlled laboratory studies involving human subjects and animals. There have been an increasing number of studies focusing on the mechanisms (that is, on learning how specific organs, cell types, and biochemicals 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 mostly pollutant-specific. This is appropriate, in that different pollutants usually 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, may sometimes act together to harm health more than they would acting separately. Nevertheless, as a practical matter, health scientists, as well as regulatory officials, usually must deal with one pollutant at a time in determining health effects and 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 toxic exposure 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 document.

This summary is drawn substantially from reviews presented previously (SCAQMD, 1996, 2003, 2007), and from reviews on the effects of air pollution by the American Thoracic Society (ATS, 1996), the U.S. EPA reviews for ozone (U.S. EPA, 2006), Carbon Monoxide (U.S. EPA, 2010), and Particulate Matter (U.S. EPA, 2004, 2009), from a published review of the health effects of air pollution (Brunekreef and Holgate, 2002), and from reviews prepared by the California EPA Office of the Environmental Health Hazard Assessment for Particulate Matter (Cal EPA, 2002) and for Ozone (Cal EPA, 2005). Additional materials are from EPA's current review of the ozone standard and health effects (EPA, 2011). More detailed citations and discussions on air pollution health effects can be found in these references.[1]

[1] Most of the studies referred to in this appendix are cited in the above sources. Only more recent specific references will be cited in this summary.

OZONE

Ozone is a highly reactive compound, and is 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, it can penetrate into the gas exchange region of the deep lung.

The EPA primary standard for ozone, adopted in 2008, is 0.075 ppm averaged over eight hours. The California Air Resources Board (CARB) has established standards of 0.09 ppm averaged over one hour and at 0.070 ppm averaged over eight hours.

The major subgroups of the population considered to be at increased risk from ozone exposure are outdoor exercising individuals, including children, and people with preexisting respiratory disease(s) such as asthma. The data base identifying the former group as being at increased risk to ozone exposure is much stronger and more quantitative than that for the latter group, probably because of a larger number of studies conducted with healthy individuals. The adverse effects reported with short-term ozone exposure are greater with increased activity because activity increases the breathing rate and the volume of air reaching the lungs, resulting in an increased amount of ozone reaching the lungs. Children may be a particularly vulnerable population to air pollution effects because they spend more time outdoors, are generally more active, and have a higher ventilation rate than adults.

A number of adverse health effects associated with ambient ozone levels have been identified from laboratory and epidemiological studies (EPA, 1996; 2006, 2011; ATS, 1996). These include increased respiratory symptoms, damage to cells of the respiratory tract, decrease in lung function, increased susceptibility to respiratory infection, and increased risk of hospitalization.

Increases in ozone levels are associated with elevated absences from school. The Children's Health Study, conducted by researchers at the University of Southern California, followed a cohort of children that live in 12 communities in Southern California with differing levels of air pollution for several years. A publication from this study reported that school absences in fourth graders for respiratory illnesses were associated with ambient ozone levels. An increase of 20 ppb ozone was associated with an 83% increase in illness-related absence rates (Gilliland, 2001).

The number of hospital admissions and emergency room visits for all respiratory causes (infections, respiratory failure, chronic bronchitis, etc.) including asthma

shows a consistent increase as ambient ozone levels increase in a community. These excess hospital admissions and emergency room visits are observed when hourly ozone concentrations are as low as 0.06 to 0.10 ppm.

Numerous recent studies have found positive associations between increases in ozone levels and excess risk of mortality. These associations persist even when other variables including season and levels of particulate matter are accounted for. This indicates that ozone mortality effects may be independent of other pollutants (Bell, 2004).

Multicity studies of short-term ozone exposures (days) and mortality have also examined regional differences. Evidence was provided that there were generally higher ozone-mortality risk estimates in northeastern U.S. cities, with the southwest and urban mid-west cities showing lower or no associations (Smith, 2009; Bell, 2008). Another long-term study of a national cohort found that long-term exposures to ozone were associated with respiratory-related causes of mortality, but not cardiovascular-related causes, when PM2.5 exposure were also included in the analysis.

Several population-based studies suggest that asthmatics are more adversely affected by ambient ozone levels, as evidenced by increased hospitalizations and emergency room visits. Laboratory studies have attempted to compare the degree of lung function change seen in age and gender-matched healthy individuals versus asthmatics and those with chronic obstructive pulmonary disease. While the degree of change evidenced did not differ significantly, that finding 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 degree of change may represent a substantially greater adverse effect overall.

Another publication from the Children's Health Study focused on children and outdoor exercise. In 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, 2002). These findings indicate that new cases of asthma in children are associated with heavy exercise in communities with high levels of ozone. While it has long been known that air pollution can exacerbate symptoms in individuals with respiratory disease, this is among the first studies that indicate ozone exposure may be causally linked to asthma onset.

In addition, human and animal studies involving both short-term (few hours) and long-term (months to years) exposures indicate a wide range of effects induced or associated with ambient ozone exposure. These are summarized in Table I-1.

TABLE I-1

Adverse Health Effects of Ozone (O3) - Summary of Key Studies

0_3 CONCENTRATION AND EXPOSURE HR., PPM	**HEALTH EFFECT**
Ambient air containing 0.10 - 0.15 daily 1-h max over days to weeks; ≥ 0.05 (8 hour average)	Decreased breathing capacity, in children, adolescents, and adults exposed to 0_3 outdoors Exacerbation of respiratory symptoms (e.g., cough, chest pain) in individuals with preexisting disease (e.g., asthma) with low ambient exposure, decreased temperature, and other environmental factors resulting in increased summertime hospital admissions and emergency department visits for respiratory causes
≥0.12 (1-3h) ≥0.06 (6.6h) (chamber exposures)	Decrements in lung function (reduced ability to take a deep breath), increased respiratory symptoms (cough, shortness of breath, pain upon deep inspiration), increased airway responsiveness and increased airway inflammation in exercising adults Effects are similar in individuals with preexisting disease except for a greater increase in airway responsiveness for asthmatic and allergic subjects Older subjects (>50 yrs old) have smaller and less reproducible changes in lung function Attenuation of response with repeated exposure
≥0.12 with prolonged, repeated exposure (chamber exposures)	Changes in lung structure, function, elasticity, and biochemistry in laboratory animals that are indicative of airway irritation and inflammation with possible development of chronic lung disease Increased susceptibility to bacterial respiratory infections in laboratory animals

From: SCAQMD, 1996; EPA, 2007

Some lung function responses (volume and airway resistance changes) observed after a single exposure to ozone exhibit attenuation or a reduction in magnitude with repeated exposures. Although it has been argued that the observed shift in response is evidence of a probable adaptation phenomenon, it appears that while functional changes may exhibit adaptation, biochemical and cellular changes which may be

associated with episodic and chronic exposure effects may not exhibit similar adaptation. That is, internal damage to the respiratory system may continue with repeated ozone exposures, even if externally observable effects (chest symptoms and reduced lung function) disappear.

In a laboratory, exposure of human subjects to low levels of ozone causes reversible decrease 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. Similar lung volume changes have also been observed in adults and children under ambient exposure conditions (0.10 - 0.15 ppm). The responses reported are indicative of decreased breathing capacity and are reversible.

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 recently summarized (Brown, 2008). As shown in the figure below, there is an increasing response on lung function with increasing exposure levels in moderately exercising subjects.

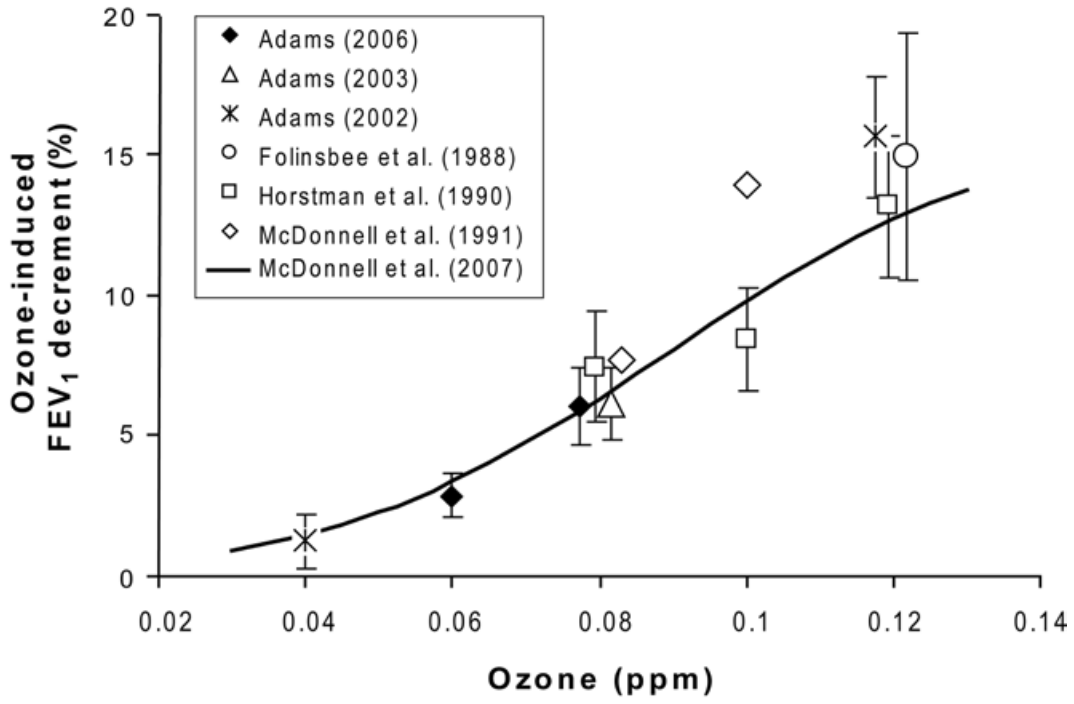

FIGURE I-1

Comparison of mean ozone-induced decrements in lung function following 6.6 hours of ozone exposure (from Brown, 2008)

In addition to controlled laboratory conditions, studies of individuals exercising outdoors, including children attending summer camp, have shown associations of reduced lung function with ozone exposure. There were wide ranges in responses among individuals.

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 (EPA, 2011).

In laboratory studies, cellular and biochemical changes associated with respiratory tract inflammation have also been consistently reported 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 cytokines and fibronectin. 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.

The susceptibility to ozone observed under ambient conditions could be due to the combination of pollutants that coexist in the atmosphere or ozone may actually sensitize these subgroups to the effects of other pollutants.

Some animal studies show results that indicate possible chronic effects including functional and structural changes of the lung. These changes indicate that repeated inflammation associated with ozone exposure over a lifetime may result in sufficient 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. An autopsy study involving Los Angeles County residents provided supportive evidence of lung tissue damage (structural changes) attributable to air pollution.

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 is 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. Confirmation by further studies is needed.

In summary, adverse effects associated with ozone exposures have been well documented, although the specific causal mechanism is still somewhat unclear.

It may be instructive to provide the overall EPA staff preliminary conclusions on the causality on ozone health effects for the health outcomes evaluated (EPA, 2011). These are provided in the two tables below.

TABLE I-2

Summary of Causal Determinations for Short-Term Exposures to Ozone

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

From EPA, 2011

TABLE I-3

Summary of Causal Determinations for Long-Term Exposures to Ozone

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

From EPA, 2011

PARTICULATE MATTER

Airborne particulates are a complex group of pollutants that vary in source, size and composition, depending on location and time. 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, may also be present.

Until several years ago, the health effects of particulates were focused on those sized 10 μm (micrometers) aerodynamic diameter and smaller. These can be inhaled through the upper airways and deposited in the lower airways and gas exchange tissues in the lung. These particles are referred to as PM10. EPA initially promulgated ambient air quality standards for PM10 of 150 $\mu g/m^3$ averaged over a 24-hour period, and 50 $\mu g/m^3$ for an annual average. EPA has since rescinded the annual PM10 standard, but kept the 24-hour standard.

In recent years additional focus has been placed on particles having an aerodynamic diameter of 2.5 μm or less (PM2.5). A greater faction of particles in this size range can penetrate and deposit deep in the lungs. The EPA recently lowered the air quality standards for PM2.5 to 35 $\mu g/m^3$ for a 24-hour average and reaffirmed 15 $\mu g/m^3$ 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 EPA promulgated the initial PM2.5 standards in 1997.

Since that time, numerous studies have been published, and some of the key studies were closely scrutinized and analyses repeated. The result is that there are now substantial data confirming the adverse health effects of PM2.5 exposures.

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 larger than 2.5 μm (often referred to as the coarse fraction) 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.

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 few years. These are generally referred to as "ultrafine" particles, with diameters of 0.1 μm or less. These particles are mainly from fresh emissions of combustion sources, but are also formed in the atmosphere from photochemical reactions. Ultrafine particles have relatively short half lives (minutes to hours) and rapidly grow through condensation and coagulation process into larger particles within the PM2.5 size range. These particles are garnering interest since laboratory studies indicate that their toxicity may be higher on a mass basis than larger particles, and there is evidence that these small particles can translocate from the lung to the blood and to other organs of the body.

There have been several reviews of the health effects of ambient particulate matter (ATS, 1996; Brunekreef, 2002; U.S. EPA, 2004; U.S. EPA, 2009). 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 (Cal EPA, 2002).

The major types of effects associated with particulate matter include:

- Increased mortality
- Exacerbation of respiratory disease and of cardiovascular disease as evidenced by increases in:
  - -Respiratory symptoms
  - -Hospital admissions and emergency room visits
  - -Physician office visits
  - -School absences
  - -Work loss days
- Effects on lung function
- Changes in lung morphology

The current federal and California standards are listed below:

TABLE I-4

Ambient Air Quality Standards for Particulate Matter

STANDARD	FEDERAL	CALIFORNIA
PM10 24-Hour average	150 μg/m^3	50 μg/m^3
PM10 Annual Average	--	20 μg/m^3
PM 2.5 24-Hour Average	35 μg/m^3	--
PM 2.5 Annual Average	15 μg/m^3	12 μg/m^3

Short-Term Exposure Effects

Epidemiological studies have provided evidence for most of the effects listed above. An association between increased daily or several-day-average concentrations of PM10 and excess mortality and morbidity is consistently reported from studies involving communities across the U.S. as well as in Europe, Asia, and South America. A review and analysis of epidemiological literature for acute adverse effects of particulate matter was published by the American Thoracic Society in 1996. Several adverse effects were listed as associated with daily PM10 exposures, as listed in Table I-5.~~undertaken by Dockery and Pope to estimate these effects as percent increase in mortality associated with each incremental increase of PM10 by 10 μg/m^3. The estimates are presented in Table I-5.~~ It also appears that individuals who are elderly or have preexistent lung or heart disease are more susceptible than others to the adverse effects of PM10 (ATS, 1996). Since then m~~M~~any more recent studies have confirmed that excess mortality and morbidity are associated with short term particulate matter levels (Pope, 2006).

Estimates of mortality effects from ~~these~~ studies of PM10 exposures range from 0.3 to 1.7% increase for a 10 μg/m^3 increase in PM10 levels. The National Morbidity, Mortality, and Air Pollution Study (NMMAPS), a study of 20 of the largest U.S. cities, determined a combined risk estimate of about a 0.5% increase in total mortality for a 10 μg/m^3 increase in PM10 (Samet, 2000a). This study also analyzed the effects of gaseous co-pollutants. The results indicated that the association of PM10 and mortality were not confounded by the presence of the gaseous pollutants. When the gaseous pollutants were included in the analyses, the significance of the PM10 estimates remained. The PM10 effects were reduced somewhat when O_3 was also considered and tended to be variably decreased when NO_2, CO, and SO_2 were

added to the analysis. These results argue that the effects are likely due to the particulate exposures; they cannot readily be explained by coexisting weather stresses or other pollutants.

An expansion of the NMMAPS study to 90 U.S. Cities also reported association with PM10 levels and mortality (Samet 2000b). It was discovered that this study was one that used a flawed statistical software package. The investigators have reanalyzed the data using corrected settings for the software (Dominici, 2002a, Dominici 2002b). When the estimates for the 90 cities in the study were recalculated, the estimate changed from 0.41% increase in mortality for a 10 $\mu g/m^3$ increase in PM10 to a 0.27% increase. There remained a strong positive association between acute exposure to PM10 and mortality. Thus while the quantitative estimate was reduced, the major findings of the study did not change.

TABLE I-5

Combined Effect Estimates of Daily Mean Particulate Pollution (PM10)

	% CHANGE IN HEALTH INDICATOR PER EACH 10 $\mu g/m^3$ 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

TABLE I-5 (concluded)

Combined Effect Estimates of Daily Mean Particulate Pollution

	% CHANGE IN HEALTH INDICATOR PER EACH 10 μg/m^3 INCREASE IN PM10
Cough	2.5
Decrease in Lung Function	
Forced expiratory volume	0.15
Peak expiratory flow	0.08

* One study only

(Source: American Journal of Respiratory and Critical Care Medicine, Vol. 153, 113-50, 1996)

Studies of PM2.5 also find associations with elevated mortality. The estimates for PM2.5 generally are in the range of 2.0 to 8.5% increase in total deaths per 25 μg/m^3 increase in 24-hour PM2.5 levels. The estimates for cardiovascular related mortality range from 3.0 to 7.0% per 25 μg/m^3 24-hour PM2.5, and for respiratory mortality estimates range from 2.0 to 7.0% per 25 μg/m^3 24-hour PM2.5.

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. Other studies in Mexico City and Santiago, Chile reported that PM10-2.5 was as important as PM2.5. Overall effects estimates for PM10-2.5 fall in the range of 0.5 to 6.0 % excess mortality per 25 μg/m^3 24-hour average.

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. More research is needed to better assess the relative effects of fine (PM2.5) and coarse (PM10-2.5) fractions of particulate matter on mortality.

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 effects estimates are generally higher than the effects for mortality. The effects are associated with measures of PM10 and PM2.5. Effects are also associated with PM10-2.5. Thus, it appears that when a relatively small number of people experience severe effects, larger numbers experience milder effects, which may relate either to the coarse or to the fine fraction of airborne particulate matter.

In the NMMAPS study, hospital admissions for those 65 years or older were assessed in 14 cities. Hospital admissions for these individuals showed an increase of 6% for cardiovascular diseases and a 10% increase for respiratory disease admissions, per 50 $\mu g/m^3$ increase in PM10. The excess risk for cardiovascular disease ranges from 3-10% per 50 $\mu g/m^3$ PM10 and from 4-10% per 25 $\mu g/m^3$ PM2.5 or PM10-2.5.

Similarly, school absences, lost workdays and restricted activity days have also been used in some studies as indirect indicators of acute respiratory conditions. The results are suggestive of both immediate and delayed impact on these parameters following elevated particulate matter exposures. These observations are consistent with the hypothesis that increased susceptibility to infection follows particulate matter exposures.

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 3% to 42% for medical visits for respiratory illnesses was found corresponding to a 50 $\mu g/m^3$ change in PM10. A limited 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.

The biological mechanisms by which particulate matter can produce health effects are being investigated in laboratory studies. Inflammatory responses in the respiratory system in humans and animals exposed to concentrated ambient particles have been measured. These include effects such as increases in neutrophils in the lungs. Other changes reported include increased release of cytokines and interleukins,

chemicals released as part of the inflammatory process. The effects of particulate matter may be mediated in part through the production of reactive oxygen species during the inflammatory process. Recent reviews discuss mechanistic studies in more detail (Brunekreef, 2002; Brook, 2004).

Long-Term Exposure Effects

While most studies have evaluated the acute effects, some studies specifically focused on evaluating the effects of chronic exposure to PM10 and PM2.5. Studies have analyzed the mortality of adults living in different U.S. cities. After adjusting for important risk factors, taken as a whole these studies found a positive association of deaths and exposure to particulate matter. A similar association was observable in both total number of deaths and deaths due to specific causes. The largest effects were observed from cardiovascular causes and ischemic heart disease. A shortening of lifespan was also reported in these studies.

Since the initial promulgation by EPA of the National Ambient Air Quality Standards for PM2.5, controversy has remained over the association of mortality and exposures to PM2.5. Thus an expanded discussion of these studies is presented below.

Significant associations for PM2.5 for both total mortality and cardiorespiratory mortality were reported in a study following a national cohort recruited by the American Cancer Society for a Cancer Preventions Study over several years. A re-analysis of the data from this study confirmed the initial finding (Krewski, 2000). In this study, mortality rates and PM2.5 levels were analyzed for 51 metropolitan areas of the U.S. Average levels from monitors in each area were used to estimate exposures. At these levels of aggregation, regional differences in the association of PM2.5 and mortality were noted, with higher associations in the Northeast, and lower or non-significant associations in the West.

The Harvard Six Cities Study evaluated several size ranges of particulate matter and reported significant associations with PM15, PM2.5, sulfates, and non-sulfate particles, but not with coarse particles (PM15 – PM2.5). An extension of the Harvard Six Cities Cohort confirmed the association of mortality with PM2.5 levels (Laden, 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 compounds. An update to this study covering a follow-up over the years 1974 to 2009 (Lepeule, 2012) was recently published. 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.

A 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 ug/m3 increase in fine particulates was associated with approximately a 4% increase in total mortality, a 6% increase in cardiopulmonary mortality, and an 8% increase risk of lung cancer mortality (Pope, 2002). The magnitude of effects is larger in the long-term studies than in the short-term investigations. In an additional re analysis and extension of the American Cancer Society cohort from 1982 to 2000 (Krewski, 2009), and including additional metropolitan areas for the most recent years, effects estimates on mortality were similar, though somewhat higher, than those reported previously.

Other national studies include an analysis of mortality and PM2.5 exposures in a Medicare population. Zeger and Associates (2008) assembled a Medicare cohort by including all Medicare enrollees residing in zip codes with centroids within 6 miles of a PM2.5 monitor. PM2.5 data was obtained from the monitoring stations, and mean annual levels were called for the zip codes within six miles of each monitor. The estimated associations between exposures to PM2.5 and mortality for the eastern and central portions of the U.S were similar to those previously published in the Six Cities Study and the American Cancer Society cohorts. The authors reported that there were no significant associations between zip code levels of PM2.5 and mortality rates in the western region of the U.S. This lack of association 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 these counties. The authors further reported that they found no associations of PM2.5 with mortality in persons aged 85 years or higher.

Analyses of mortality and PM2.5 levels specific to California have also been reported. A cohort of elderly individuals (average age of 65 yr in 1973) recruited from 11 California counties was followed over several years (Enstrom, 2005). An association for exposure with all cause deaths was reported from 1973–1982. However, no significant association was found in the later time period of 1983–2002. Pollutant levels were taken from ambient monitors and averaged over each county to estimate exposures.

Two analyses of the American Cancer Society cohort 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. Using data from monitoring stations in the Los Angeles area, one study applied interpolation methods (Jerrett, 2005) and another applied land use regression techniques (Krewski, 2009) to estimate exposures to the study individuals. Significant associations of PM2.5 with mortality from all causes and cardiopulmonary disease were reported, with the magnitude of risks being up to three times higher than those from the national studies of the American Cancer Society cohort. This provides evidence that using methods to provide more detailed exposure estimates can result in stronger associations of PM2.5 and mortality.

~~Two~~ recent reports have been released looking at air pollution and health effects in California. One study (Lipsett, 2011) followed school teachers recruited in 1995, and followed through 2005. Pollutant exposures at the subject residence were estimated using data from ambient monitors, and extrapolated using a distance weighted method. The authors reported significant association of PM2.5 levels and mortality from ischemic heart disease, but no associations were found with all cause, cardiovascular, or respiratory disease.

The second study (Jerrett, 2011) followed individuals in ~~the Los Angeles area~~ California from the American Cancer Society cohort recruited starting in 1982, with follow up to 2000. Pollutant levels at subject residences were estimated using several methods. All but one of the methods found no association of all-cause mortality with PM2.5 levels. All exposure estimation methods were reported to have found significant associations with ischemic heart disease mortality, however. The authors noted that mortality rates differ in urban areas compared to non-urban areas, and so included a variable for this in a land use regression model to estimate effects on mortality. When the authors applied the land use regression model including an urban indicator to estimate exposures, all-cause mortality, mortality from cardiovascular disease, and mortality from ischemic heart disease were all significantly associated with PM2.5 levels.

The U.S. EPA has recently proposed to lower the annual National Ambient Air Quality Standard for PM2.5 (U.S. EPA, 2012a). EPA also released a Regulatory Impact Analysis (U.S. EPA 2012b)which looked at the costs and benefits of alternate PM2.5 stand levels. As part of the analysis, EPA also looked at California specific studies regarding PM2.5 and mortality published in the scientific literature. The 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 cohort studies conducted in California indicate higher risks than the risk estimates we applied." Thus in EPAs judgment the California related studies provided estimates of mortality consistent with or higher than those from the national studies.

Other studies report evidence indicating that particulate matter exposure early in pregnancy may be associated with lowered birth weights (Bobak, 1999). Studies from the U.S., the Czech Republic and Mexico City have reported that neonatal and early postnatal exposure to particulate matter may lead to increased infant mortality. A more recent study in Southern California found increased risks for infant deaths associated with exposures to particulates and other pollutants (Ritz, 2006). These results suggest that infants may be a subgroup affected by particulate matter exposures.

In addition, some long-term effect studies have reported an increased risk of mortality from lung cancer associated with particulate matter exposures. A study involving California Seventh Day Adventists (very few of whom smoke) has reported an association of lung cancer mortality with PM10 levels. It is not clear from these studies whether the association relates to causation of disease, or whether individuals with cancer are more susceptible to other effects of particles leading to the observed mortality association. A study that followed a large number of individuals living in the largest U.S. cities found elevated lung cancer risk associated with long-term average PM2.5 levels (Pope, 2002).

Several studies have assessed the effects of long-term particulate matter exposure on respiratory symptoms and lung function changes. Associations have been found with symptoms of chronic bronchitis and decreased lung function. A study of school children in 12 communities in Southern California showed significant association of particulate matter with bronchitis or phlegm in children with asthma. These effects were also associated with NO_2 and acid vapor levels

A cohort of fourth graders from the Southern California communities was followed over a period of four years by the Children's Health Study. A lower rate of growth in lung function was found in children living in areas with higher levels of particulate pollution (Gauderman, 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, 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 regain some of the lung function growth rate (Avol, 2001). By the time the fourth graders graduated from high school, a significant number showed lower lung function. The risk of lower lung function was about five times higher in children with the highest PM2.5 exposure when compared to the lowest exposure communities (Gauderman, 2004). These deficits are likely to persist since the children were at the end of their growth period.

Despite data gaps, the extensive body of epidemiological studies has both qualitative and quantitative consistency suggestive of causality. A considerable body of evidence from these studies suggests that ambient particulate matter, alone or in combination with other coexisting pollutants, is associated with significant increases in mortality and morbidity in a community.

In summary, the scientific literature indicates that an increased risk of mortality and morbidity is associated with particulate matter at ambient levels. 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.

EPA staff has presented conclusions on causal determination of several health effects based on a recent review of the available scientific studies (EPA, 2009). These are depicted in the Table below.

TABLE I-6

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

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

From EPA, 2009

ULTRAFINE PARTICLES

As noted above, numerous studies have found association of particulate matter levels with adverse effects, including mortality, hospital admissions, and respiratory disease symptoms. The vast majority of these studies used particle mass of PM10 or PM2.5 as the measure of exposure. Some researchers have postulated, however, that ultrafine particles may be responsible for some of the observed associations of particulate matter and health outcomes (Oberdorster, et al, 1995; Seaton, et al, 1995). Ultrafine particles are generally classified of 0.1 μm and small diameter.

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

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

Smaller particles can also be inhaled deep into the lungs. As much as 50% of 0.02 µm diameter particles are estimated to be deposited in the alveolar region of the lung. There is complex nature of the relation between deposition and particle size. The ultrafine particles generally have higher fractional deposition in the alveolar region. However, for the smaller nucleation mode (particles less than 0.01 µm size) the deposition in the alveolar region declines, but increases in the extrathoracic region.

Exposures of laboratory animals to ultrafine particles have found cardiovascular and respiratory effects. Mice exposed to concentrated near roadway ultrafine particles showed larger early atherosclerotic lesions than mice exposed to PM2.5 or filtered air (Arujo, 2008). In a mouse allergy model, exposures to concentrated ultrafine particles resulted in a greater response to antigen challenge to ovalbumin (Li, 2010), indicating that vehicular traffic exposure could exacerbate allergic inflammation in already-sensitized animals.

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, 2011, for example found exposure to diesel exhaust particulate attenuated both acetylcholine and sodium-nitroprusside -induced vasorelaxation.

There are no long-term studies of human population exposure to ultrafine particle, as there is a lack of a monitoring network in the U.S. There have been several cross sectional epidemiological studies of ultrafine particles, mainly from Europe. Some of these studies found effects on hospital admissions, emergency department visits, for respiratory and cardiovascular effects. Other studies, however, have not found such effects (EPA, 2009). Concentrations of ultrafine particles can vary geographically, and it is not clear how well central site monitors may capture actual exposures.

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 (EPA, 2009). These are depicted in the table below.

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

TABLE I-7

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

SHORT-TERM EXPOSURES	
Health Outcome	**Causality Determination**
Cardiovascular effects	Suggestive
Respiratory effects	Suggestive
Central nervous system	Inadequate information to assess
Mortality	Inadequate
LONG-TERM EXPOSURES	
Health Outcome	**Causality Determination**
Cardiovascular effects	Inadequate
Respiratory effects	Inadequate
Mortality	Inadequate
Reproductive and developmental	Inadequate
Cancer, Mutagenicity, Genotoxicity	Inadequate

From EPA, 2009

CARBON MONOXIDE

The high affinity of carbon monoxide (CO) to bond with oxygen-carrying proteins (hemoglobin and myoglobin) results in reduced oxygen supply in the bloodstream of exposed individuals. The reduced oxygen supply 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 (U.S. EPA, 2000, 2010).

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). Exposure to CO is often evaluated in terms of COHb levels in blood measured as percentage of total hemoglobin bound to CO. COHb levels in non-smokers range between 0.3 and 0.7% and 5 to 10% in smokers. COHb levels in excess of 1.5% in a significant proportion of urban non-smoking populations can be considered as evidence of widespread exposure to environmental CO.

Under controlled laboratory conditions, healthy subjects exposed to CO sufficient to result in 5% COHb levels exhibited reduced duration of maximal exercise performance and consumption of oxygen. Studies involving subjects with coronary artery disease who engaged in exercise during CO exposures have shown that COHb levels as low as 2.4% can lead to earlier onset of electrocardiograph changes indicative of deficiency of oxygen supply to the heart. Other effects include an earlier onset of chest pain, an increase in the duration of chest pain, and a decrease in oxygen consumption.

Findings of epidemiologic studies have observed associations between ambient CO concentration and emergency department visits and hospital emissions for ischemic heart disease and other cardiovascular diseases.

Animal studies associated with long-term exposure to CO resulting in COHb levels that are equivalent to those observed in smokers have shown indication of reduction in birth weight and impaired neurobehavior in the offspring of exposed animals.

Epidemiological studies conducted in Southern California have indicated an association with CO exposure during pregnancy to increases in pre-term births. (Ritz, 2000). However, the results were not consistent in different areas studied. The increase in the pre-term births was also associated with PM10 levels. Another study found increased risks for cardiac related birth defects with carbon monoxide exposure in the second month of pregnancy (Ritz, 2002). Toxicological studies in laboratory animals with higher than ambient levels of CO have also reported decrements in birth weight and prenatal growth.

EPA staff has presented conclusions on causal determination of the health effects of carbon monoxide based on a recent review of the available scientific studies (EPA, 2010). These are depicted in the table below.

TABLE I-8

Causal Determination for Health Effects of Carbon Monoxide

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

From EPA, 2010

NITROGEN DIOXIDE

The U.S. EPA has recently reviewed the health effects of nitrogen dioxide (U.S. EPA, 2008a). Evidence for low-level nitrogen dioxide (NO_2) exposure effects is derived from laboratory studies of asthmatics and from epidemiological studies. Additional supportive evidence is derived from animal studies.

Epidemiological studies using the presence of an unvented gas stove as a surrogate for indoor NO_2 exposures suggest an increased incidence of respiratory infections or symptoms in children.

Recent studies related to outdoor exposure have found health effects associated with ambient NO_2 levels, including respiratory symptoms, respiratory illness, decreased lung function, increased emergency room visits for asthma, and cardiopulmonary mortality. However, since NO_2 exposure generally occurs in the presence of other pollutants, such as particulate matter, these studies are often unable to determine the specific role of NO_2 in causing effects.

The Children's Health Study in Southern California found associations of air pollution, including NO_2, PM10, and PM2.5, with respiratory symptoms in asthmatics (McConnell, 1999). Particles and NO_2 were correlated, and effects of individual pollutants could not be discerned. A subsequent analysis indicated a stronger role for NO2 (McConnell, 2002).

Ambient levels of NO_2 were also associated with a decrease in lung function growth in a group of children followed for eight years. In addition to NO_2, the decreased growth was also associated with particulate matter and airborne acids. The study authors postulated that these may be a measure of a package of pollutants from traffic sources. (Gauderman, 2004).

Results from controlled exposure studies of asthmatics demonstrate an increase in the tendency of airways to contract in response to a chemical stimulus (bronchial reactivity). Effects were observed with exposures from 0.1 to 0.3 ppm NO_2 for periods ranging from 30 minutes to 3 hours. A similar response is reported in some studies with healthy subjects at higher levels of exposure (1.5 - 2.0 ppm). Mixed results have been reported when people with chronic obstructive lung disease are exposed to low levels of NO_2.

Short-term controlled studies of animals exposed to NO_2 over a period of several hours indicate cellular changes associated with allergic and inflammatory response and interference with detoxification processes in the liver. In some animal studies

the severity of the lung structural damage observed after relatively high levels of short-term ozone exposure is observed to increase when animals are exposed to a combination of ozone and NO_2.

In animals, longer-term (3-6 months) repeated exposures at 0.25 ppm appear to decrease one of the essential cell-types (T-cells) of the immune system. Non-specific changes in cells involved in maintaining immune functions (cytotoxic T-cells and natural killer cells) have been observed in humans after repeated exposure (4-6 days) to >0.6 ppm of NO_2 (20 min. - 2 hours). All these changes collectively support the observation reported both in population and animal studies of increased susceptibility to infections, as a result of NO_2 exposure.

The U.S. EPA recently adopted a new short-term standard of 100 ppb (0.1 ppm) averaged over 1 hour. The standard was designed to protect against increases in airway reactivity in individuals with asthma observed in controlled exposure studies, as well as respiratory symptoms observed in epidemiological studies.

SULFUR DIOXIDE

Controlled laboratory studies involving human volunteers have clearly identified asthmatics as the most 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 significant alteration of lung function, such as increases in airway resistance and decreases in breathing capacity. In some, the exposure can result in severe symptoms necessitating the use of medication for relief. The response to SO_2 inhalation is observable within 2 minutes of exposure, increases further with continuing exposure up to 5 minutes then remains relatively steady as exposure continues. SO_2 exposure is generally not associated with any delayed reactions or repetitive asthmatic attacks.

In epidemiologic studies, associations of SO_2 levels with increases in respiratory symptoms, increases in emergency department visits and hospital admissions for respiratory-related causes have been reported.

The U.S. EPA has recently revised the SO_2 air quality standard. The previous 24-hour standard was rescinded and replaced with a new 1-hour standard at 75 ppb (0.075 ppm) to protect against high short-term exposures.

Animal studies have shown that despite SO_2 being a respiratory irritant, it does not cause substantial acute or chronic toxicity in animals exposed at ambient concentrations. However, relatively high exposures (10 ppm of SO_2 for 72 hours) in mice can lead to tissue damage, fluid accumulation and sloughing of respiratory lining. Sensitization to allergies is observable in guinea pigs repeatedly exposed to high levels (72 ppm) of SO_2. This effect needs further evaluation in clinical and population studies to identify any chronic exposure impact on both asthmatic incidence and attacks in a population.

Some epidemiological studies indicate that the mortality and morbidity effects associated with the fine fraction of particles show a similar association with ambient SO_2 levels. In these studies, efforts to separate the effects of SO_2 from fine particles have not been successful. Thus, it is not clear whether the two pollutants act synergistically, or whether being generated from similar combustion sources, they represent the same pollution index for the observed effects.

SULFATES

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.

In recent years, a vast majority of effects (mortality and morbidity) associated with fine particles (PM2.5) and sulfur dioxide have shown a similar association with ambient sulfate levels in some population studies. The efforts to fully separate the effects of sulfates from other coexisting pollutants have not been successful. This may be due to the fact that these pollutants covary under ambient conditions, having been emitted from common sources; and the effects observed may be due to the combination of pollutants, rather than a single pollutant.

A clinical study involving exposure of human subjects to sulfuric acid aerosol indicated that adolescent asthmatics may be a susceptible population subgroup with some changes in lung function observed with exposures below 100 $\mu g/m^3$. In general, however, laboratory exposures of human volunteers to sulfates at or near ambient levels have not found significant changes in lung function.

Results from animal studies involving exposures to sulfuric acid aerosol, ammonium bisulfate and ammonium sulfate indicate that acidic particles (former two) are more toxic than non-acidic particles (latter). In addition, the severity or magnitude of both

mortality and morbidity effects is relatively higher in population studies of the eastern United States and Canada where sulfate concentrations are higher than for those observed in the western United States. Mixed results have been reported from studies which attempted to ascertain the role of acidity in determining the observed toxicity.

LEAD

The U.S. EPA has recently reviewed the health effects of ambient lead exposures in conjunction with a review of the NAAQS for lead. (U.S. EPA 2006b; U.S. EPA 2007b). The following summary is taken from these reviews.

There are a number of potential public health effects at low level exposures. The health implications are generally indexed by blood lead levels, which are related to lead exposures both from inhalation as well as from ingestion. As identified by EPA, effects includeimpacts on population IQ, as well as heart disease and kidney disease. The array of health effects includes the following.

- Heme biosynthesis and related functions;
- Neurological development and function;
- Reproduction and physical development;
- Kidney function;
- Cardiovascular function
- Immune function

Children appear to be sensitive to the neurological toxicity of lead, with effects observed at blood lead concentration ranges of 5 – 10 µg/dL, or possibly lower. No clear threshold has yet been established for such effects.

According to the 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.

EPA has recently revised the NAAQS for lead to a level of 0.15 µg/m^3 averaged over a 3 month period to protect against lead toxicity. The following two charts, taken from the U.S. EPA review, depict the health effects of lead in relation to blood levels.

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

FIGURE I-2

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

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				

FIGURE I-3

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

TOXIC AIR CONTAMINANTS

Toxic air contaminants are pollutants for which there generally are no ambient air quality standards. Under California's Air Toxics Program, CARB staff and Office of Environmental Health Hazard Assessment (OEHHA) assess the health effects of substances that may pose a risk of adverse health effects. These effects are usually an increased risk for cancer or adverse birth outcome. 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.

CARB and OEHHA also establish 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.

The District conducted studies on the ambient concentrations and estimated the potential health risks from air toxics (SCAQMD, 2008). In the latest study, a two year monitoring program was undertaken at 10 sites throughout the SCAB over the time period 2004-2006. Over 30 substances were measured, and annual average levels were calculated. The results showed that the overall risk for excess cancer from a 70-year lifetime exposure to the levels of air toxics calculated as the average level at the 10 sites was about 1,200 in a million. The largest contributor to this risk was diesel ~~exhaust~~particulate matter, accounting for about 84% of the air toxics risk. A breakdown of the major contributors to the air toxics risk is shown in ~~FIGURE I-2~~FIGURE I-4.

While the California Air Resources Board listed Diesel Particulate Matter as a Toxic Air Contaminant in 1989, the International Agency for Research on Cancer, an arm of the World Health Organization, recently convened an international panel of scientists to review the published literature regarding the carcinogenicity of diesel combustion emissions. The panel concluded that Diesel Exhaust is a substance that causes cancer in humans (Benbrahim-Tallaa, 2012).

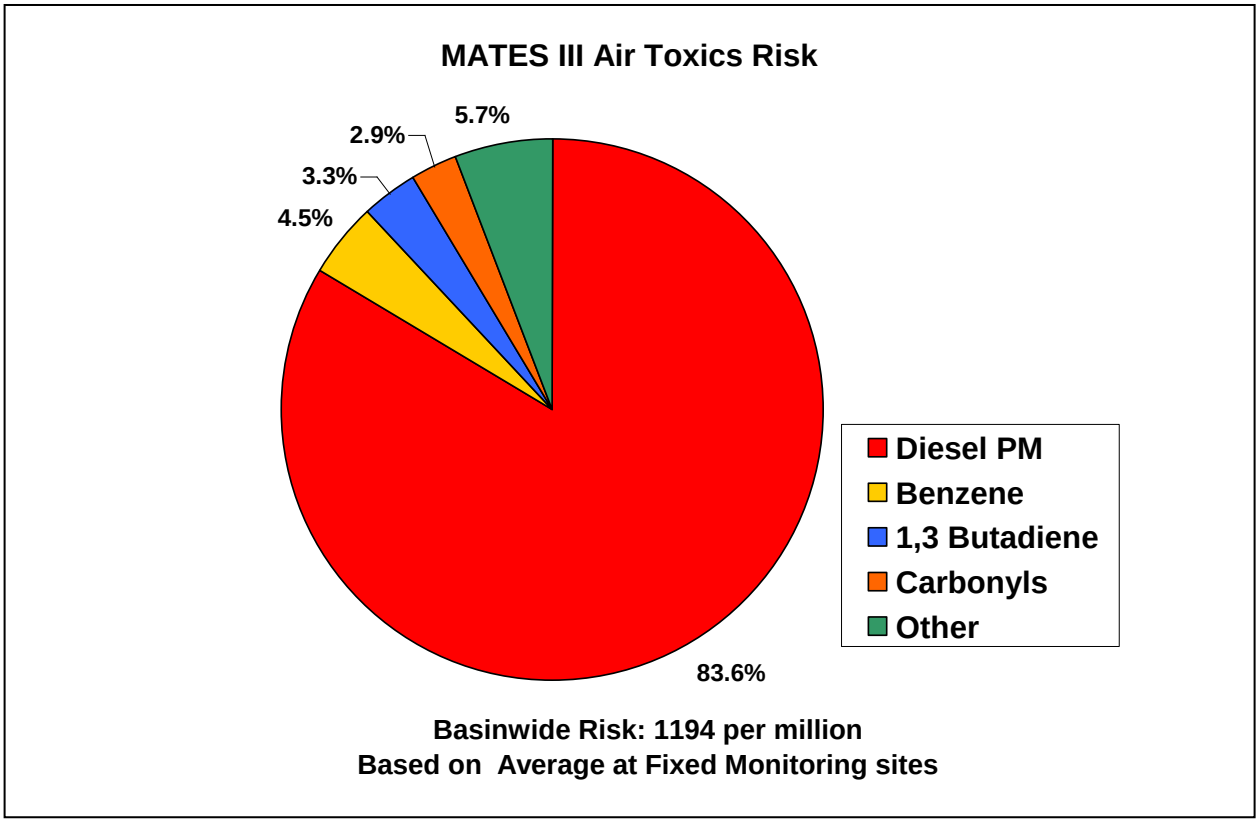

FIGURE I-4~~2~~

Major Pollutants Contributing to Air Toxics Cancer Risk in the South Coast Air Basin

For non-cancer health effects, OEHHA has developed acute and chronic Reference Exposure Levels (RELs). RELs are concentrations in the air below which adverse health effects are not likely to occur. Acute RELs refer to short-term exposures, generally of one-hour duration. Chronic RELs refer to long-term exposures of several years. 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. The measured levels from the most recent study were below the applicable Reference Exposure Levels.

The key air toxics contributing to risk from mobile and stationary sources are listed in TABLE I-9.

TABLE I-9

Key Toxic Air Contaminants in the SCAB

MOBILE SOURCES	STATIONARY SOURCES
Acetaldehyde	Hexavalent Chromium
Benzene	Methylene Chloride
1,3 Butadiene	Nickel
Diesel ~~Exhaust~~Particulate Matter	Perchloroethylene
Formaldehyde	Trichloroethylene

CONCLUSION

A large body of scientific evidence shows that the adverse impacts of air pollution in 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, earlier mortality ~~and air pollution~~.

As the scientific methods for the study of air pollution health effects has progressed over the past decades, adverse effects have been shown to occur at lower levels of exposure. For some pollutants, no clear thresholds for effects have been demonstrated. The new findings have, in turn, led to the revision and lowering of National Ambient Air Quality Standards which, in the judgment of the Administrator of the U.S. EPA, are necessary to protect public health. The figures below are meant to convey some of the historical context to recent revisions to the NAAQS for ozone and for particulate matter.

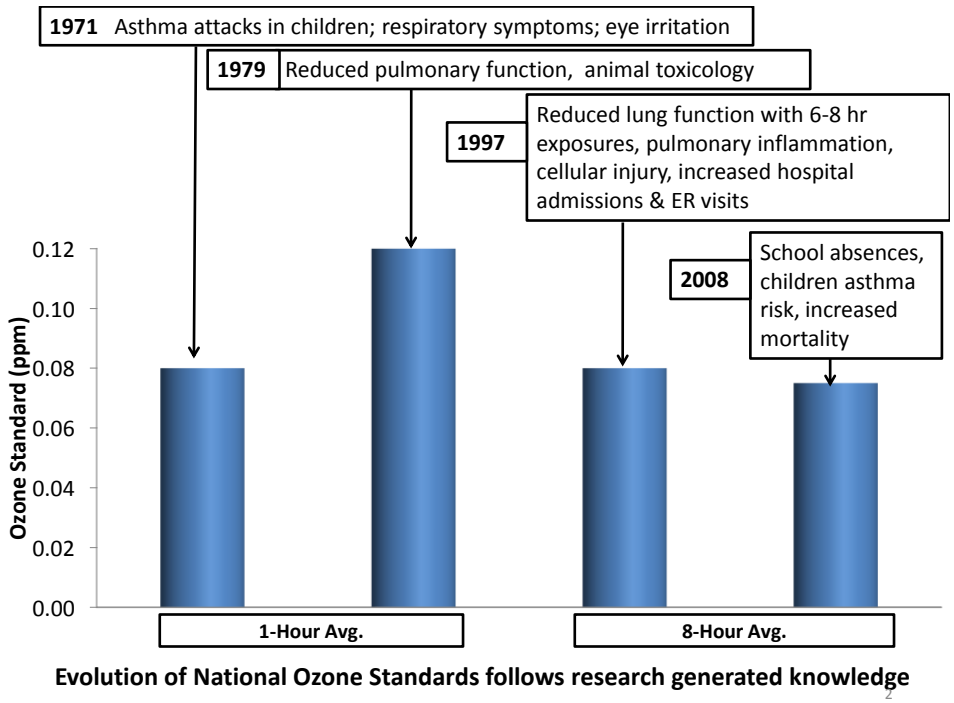

FIGURE I-4

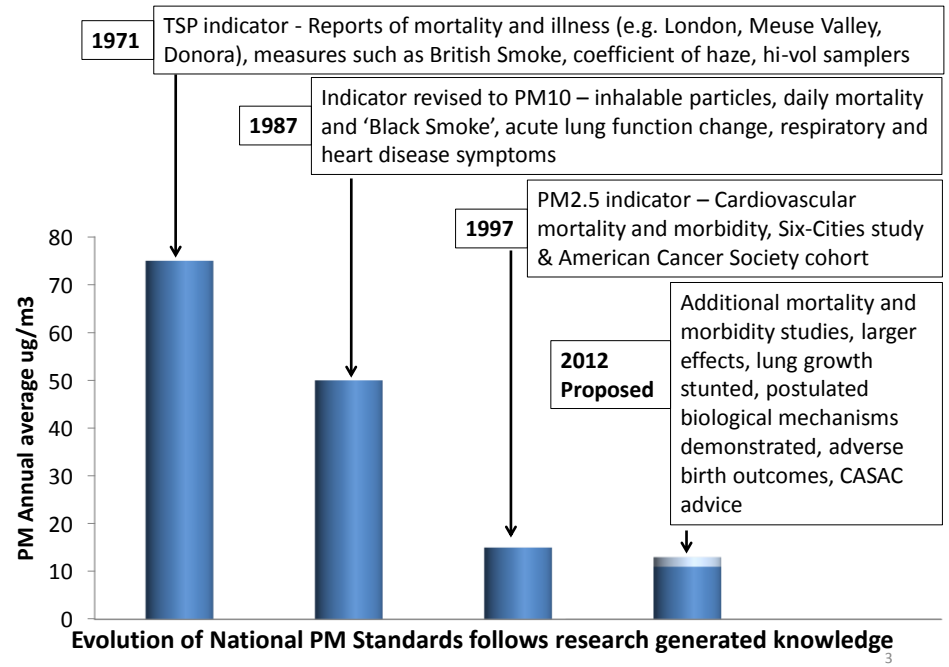

FIGURE I- 5

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ATTACHMENT 3

COMMENTS RECEIVED ON DRAFT APPENDIX I FROM SCAQMD ADVISORY COUNCIL

Section 40471 of the California Health and Safety Code calls for the periodic preparation of a report on the health impacts of particulate matter air pollution in the South Coast Air Basin as part of the Air Quality Management Plan (AQMP) revisions. The report is to be submitted to the Advisory Council for review and comment.

The correspondence requesting comments from the Advisory Council and a copy of their comments received through October 5, 2012, follow.

-----Original Message-----
From: Jean Ospital
Sent: Thursday, June 07, 2012 11:47 AM
To: Afif El-Hasan (Afif.h.el-hasan@kp.org); David Czamanske (dczamanske@hotmail.com); Ed Laird (elaird@coatingsresource.com); Emily Nelson (dremilynelson@gmail.com); makeoverearth.com, gary; Greg Adams (gadams@lacsd.org); J. Wayne Miller (wayne.miller@ucr.edu); John Froines (jfroines@ucla.edu); Lester, Julia; Mike Wang (mwang@wspa.org); radtech.org, rita; Robert McConnell (rmcconne@usc.edu); Sam Soret (ssoret@llu.edu); Todd Campbell (tcampbell@cleanenergyfuels.com); Walter Siembab (ws@siembab.com); William LaMarr (BillLaMarr@msn.com)
Cc: Elaine Chang; Barbara Baird; Michael Krause; Marilyn Traynor
Subject: Review of Health Effects - 2012 AQMP Draft Appendix I

Greetings to all,

I want to thank all of you for agreeing to participate on the AQMD's Advisory Council, and provide an update to our schedule.

As you know, Section 40471 of the California Health and Safety Code calls for the periodic preparation of a report on the health impacts of particulate matter air pollution in the South Coast Air Basin as part of the Air Quality Management Plan (AQMP) revisions. The report is to be submitted to the Advisory Council for review and comment.

We have prepared a draft of the report on PM2.5, which also includes other air pollutant health impacts, as a draft Appendix I to the 2012 AQMP. The draft Appendix I is attached for your review.

We have scheduled a meeting of the Advisory Council to provide comments to District staff. The details are below.

Date: Wednesday, July 11, 2012
Time: 2:00 p.m.-4:00 p.m.
Place: SCAQMD Conference Room CC-8

Please send any written comments you might have to me by July 11, 2012. Electronic format is preferred. All comments received will be attached to the Appendix when it is released in final form.

The Advisory Council is subject to the California open meetings regulations. Please do not copy other Advisory Council members regarding your comments. There will be opportunity for discussion at the meeting on July 11. The Advisory Council Roster is attached for your information.

Thanks again, and please let me know if I can provide any additional information.

Jean Ospital
Health Effects Officer
South Coast Air Quality Management District
21865 Copley Drive
Diamond Bar, CA 91765
Phone: 909-396-2582
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Chief Engineer and General Manager

July 10, 2012
File No.: 31-380.10

Jean Ospital, Dr.P.H.
South Coast Air Quality Management District
21865 Copley Drive
Diamond Bar, California 91765-4182

Dear Dr. Ospital:

Comments on Appendix I: Health Effects
Draft 2012 Air Quality Management Plan

Thank you for the opportunity to represent Los Angeles County Sanitation Districts and Supervisor Antonovich in submitting these brief comments on Appendix I of the 2012 Draft Air Quality Management Plan. As you well know, the AQMP presents varying degrees of significant impacts on all the residents of the air basin, and we recognize the staff's considerable efforts to address many of those in the AQMP as specifically as possible and applaud your efforts. We have the following comments on Appendix I and the health aspects draft 2012 AQMP.

1. Consider implementing the most beneficial control measures healthwise-speaking first. While there is the obligatory ranking of control measures with respect to cost effectiveness, another permutation on this might be showing the reduction in population exposure per control measure, if such a calculation can be made. Implementing the most beneficial measures healthwise first might also garner more popular support for the plan.

2. We raised a concern as to the focus of air toxics measures in the 2007 AQMP and are not certain we ever got a response and will take this opportunity to raise it again. On Page I-25 of the 2012 Appendix I, the basinwide cancer risk is reported to be 1200 in a million, largely the impact of Diesel particulate matter and other mobile source emissions. We also look again at Dr. Thomas Mack's 2004 work Cancers in the Urban Development[1], a detailed study "atlas" of three quarters of a million cancer types reported to the Cancer Surveillance Program at USC by mostly L.A. County doctors between 1972 and 1998. With the exception of high-risk tracts around the 405, 605,105, and 710 freeways and some areas between the two ports (we will return to this) the L.A. County rates for nose and throat, all types of lung and bronchus carcinomas, papillary

[1] Cancers in the Urban Environment *Patterns of Malignant Disease in Los Angeles County and Its Neighborhoods*; Thomas Mack, Dept. of Preventive Medicine, Keck School of Medicine, Norris Comprehensive Cancer Center, University of Southern California; Elsevier Academic Press, 2004.

carcinoma of the thyroid, squamous bladder carcinoma, diffuse mixed B-cell non-Hogkin lymphoma were similar to the national rate while prostrate carcinoma, brain malignancies, small cell carcinoma of the lung and bronchus, adenocarcinoma of the lung and bronchus were slightly lower than the national rate. In the last paragraph on Page 7 of the 645 page tome, in a section entitled *Environmental and Other Causes of Cancer* the author states,"...no local increase in cancer due to pollution has yet been clearly identified in the United States. Even such highly publicized sites of pollution as the Love Canal, Three Mile Island and those popularized in the movies *Erin Brockovich* and *A Civil Action* did not produce clear evidence of a cancer excess, although each of these examples of irresponsible industrial contamination represented a clear potential danger to local residents and may have produced other medical problems." In the very last sentence of that same book on Page 645, Dr. Mack also states, "As of this writing, no evidence of a malignancy caused by a strictly environmental carcinogen has yet been confirmed."

Several types of cancers unfortunately seem more prevalent around certain freeways and between the ports and these are worthy of more study. We believe the AQMP should focus on acute and chronic effects of non-carcinogenic air pollution as a priority, while the localized impacts around freeways and ports is further studied for their carcinogenic health effects.

3. We believe that some analysis of indoor air quality and the PM2.5 attainment plan is appropriate at this time. A significant portion of human exposure to PM2.5 occurs indoors where people spend ~85-90% of their time.[2]

We thank you for this opportunity to comment.

Very truly yours,

Grace Robinson Chan

Gregory M. Adams

Gregory M. Adams
Assistant Departmental Engineer
Air Quality Engineering
Technical Services Department

GMA:bb

cc: Debbie Mendelsohn

[2] Journal of the Air and Waste Management Association, March 2007, *Indoor/Outdoor Relationships, Trends, and Carbonaceous Content of Fine Particulate Matter in Retirement Homes of the Los Angeles Basin,* p.366.

From: Afif Elhasan
To: Jean Ospital
Cc: Elaine Chang
Subject: AQMP comments-Elhasan
Date: Tuesday, July 10, 2012 5:59:42 AM
Attachments: AQMP-Elhasan1.doc

I'll see you at the meeting tomorrow. Attached are some comments.

best regards-afif

Comments on the “Draft 2012 AQMP Appendix I-Health Effects”

From Afif El-Hasan, MD, Member-Environmental Justice Committee, AQMD

The 2012 AQMP Draft Report on Health Effects summarized the deleterious effects of a number of airborne pollutants. I would like to make the following comments:

Lower income populations tend to live in closer proximity to freeways, large volume transportation corridors or other sources of man-made air pollution. Other factors compounding the issue include reduced use of air conditioning (more open windows) and less use of auto transportation (more walking in polluted areas and using bikes/buses). This population also has less access to routine medical care, inhaled anti-inflammatory medication for chronic lung disease, and antibiotics for infection. These environmental and socioeconomic factors must be taken into account in future population studies on the effects of air pollution.

Obesity must be addressed in these studies. Decreased activity due to poor outside air quality, lung disease, asthma, and lack of access to healthier (more expensive) food are all contributors to obesity. In turn, obesity increases the prevalence of asthma, lung disease, cardiovascular disease and cancer. Physical activity then becomes further decreased which leads to further health issues. Fat cells can also store lipid soluble chemicals that are absorbed from the environment. This may possibly contribute to the body’s deterioration with chronic exposure to pollutants.

Pregnancy is another unique and serious issue. Pregnancy is associated with reduced lung function at a time when the mother’s lungs and cardiovascular system are supporting both the mother and the child. At the same time, the fetus is vulnerable to chemical exposure at a critical time in development. The human toll to the family of a baby with health problems and the cost to society of a premature infant or an infant with birth defects makes protection of the pregnant women a priority from a public health standpoint.

Studies have suggested a decrease in mental function associated with exposure to air pollution. This has been documented in adults with chronic exposure to high levels of air pollution, and in children born and raised in these areas. When establishing values for safe levels of pollution in the air, risks to cognitive function must be addressed. This is especially important for children who may attend schools or use parks that are in close proximity to freeways and other transportation corridors.

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July 11, 2012

Jean Ospital, Dr. P.H.
Health Effects Officer
South Coast Air Quality Management District
21865 Copley Drive
Diamond Bar, CA 91765

Subject: Comments on Appendix I Draft 2012 Air Quality Management Plan

Dear Dr. Ospital:

I appreciate the opportunity to represent the Home Rule Advisory Group (HRAG) in submitting comments on the draft report on $PM_{2.5}$, and other air pollutant health impacts, as they are set forth in Appendix I of the 2012 Draft Air Quality Management Plan (AQMP). Speaking on behalf of the HRAG, we understand that the AQMP promises to have significant impacts on all who are participating in the process and applaud the time and effort required to produce a thorough and feasible plan.

Following are my comments:

In the draft, considerable effort has gone into explaining the adverse health effects associated with exposure to air pollutants and toxic air contaminants and linking it with increases in illness (morbidity) and increases in death rates (mortality). On Page I-25, for example, the report states that the cancer risk throughout the South Coast Air Basin (SCAB) is 1200 in a million and largely attributable to diesel exhaust from mobile sources, accounting for as much as 84% of the air toxics risk. This is confirmed by the chart (Figure 2) on Page I-26, showing "*Major pollutants contributing to Air Toxics Cancer Risks in the South Coast Air Basin,*" and Table 9, on Page I-26: "*Key Toxic Air Contaminants in the SCAB.*"

While stationary sources and mobile sources contribute to the overall cancer risk, clearly, the latter is the major contributor and should warrant the greatest and most immediate attention from a regulatory, as well as a health effects perspective. It has been discouraging, from our participation in the AQMP Advisory Group meetings, to learn that suggested strategies for reducing diesel exhaust from mobile sources seem to be more voluntary than prescriptive and don't appear to have the same degree of urgency as those for stationary sources.

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We also noticed that a number of reviews, analyses and studies on the effects of air pollution, ozone, and particulate matter are cited throughout the report. Some of this research was done on a national and international level, and some was done in specific cities throughout the United States. One study which is specific to California, and involved a cohort of individuals from 11 California counties, was conducted by Dr. James E. Enstrom, and represents a contrarian perspective of the $PM_{2.5}$ and mortality relationship. Little coverage of the study, and the significance of the findings, is given in the report. Other relevant scientific data which can be found in research by Dr. Robert Phalen's book: "*The Particulate Air Pollution Controversy*" would be a useful and instructive addition to the final version of this report. One other body of research which has been completely overlooked or disregarded in this report is "*Cancers in the Urban Environment*," by Dr. Thomas M. Mack.

This research appears to be extremely relevant because it is focused on patterns of malignant disease in Los Angeles County and its neighborhoods. In his book, Dr, Mack discusses many cases involving nonrandom, geographic variations, thus indicating that factors other than chance determine the pattern of community incidence. Among the factors known to be responsible for individual malignancies are personal experiences other than occupational exposures. Some of these are habits, recreational preferences, past reproductive and medial events, and genetic inheritance.

In at least six instances in his book the geographic distribution of high risk of disease was clearly nonrandom, but did not conform to the pattern that would have been predicted by available knowledge. The malignancies in question included oropharyngeal carcinoma, small cell carcinoma and adenocarcinoma of the lung, papillary carcinoma of the thyroid, squamous carcinoma of the bladder, and diffuse mixed B-cell non-Hodgkin lymphoma. According to Dr. Mack, the true explanation for none of these patterns is currently known, although educated guesses provide tentative hypotheses that are currently still be evaluated. As a final statement in his book, Dr. Mack states that "*as of this writing, no evidence of a malignancy caused by a strictly environmental carcinogen has yet been confirmed.*"

In December 2006, when commenting on the 2007 AQMP, I raised a concern about the methodology used by a district consultant when attempting to quantify the health effects from improvements in levels of $PM_{2.5}$ and ozone and assigning economic values to those same health effects for that AQMP. Our comments were made out of concern for the environment, as well as for the health and welfare of the workforce, our families, and the general public. Another reason for expressing my concern and commenting on this aspect of the 2007 AQMP was over the alarming and ever increasing cost of compliance with the rules that are ultimately promulgated after every AQMP. Just as the cost of health care continues to rise, so does the cost of compliance.

We were encouraged to read on Page I-13 of the report that the district acknowledges that more research is needed to better assess the relative effects of fine ($PM_{2.5}$) and coarse ($PM_{10-2.5}$) fractions of particulate matter on mortality. It is common knowledge that the district and much if not all of the business community differs over the methodology used to measure the costs and

benefits associated with certain emissions and/or risk reduction strategies. We hope that these differences can be quickly and amicably resolved.

As a way of emphasizing the importance of realistically measuring costs and benefits for control strategies, I would like to mention that at the time the 2007 AQMP was being drafted the unemployment rate in the Los Angeles County was 4.7%. The 2007 Budget Act signed by then Governor Schwarzenegger included the largest reserve of any budget act in the state's history. Today, while the state of our air quality continues to improve the state of our economy and the availability of jobs has worsened. If the goal of the AQMP is to improve air quality, reduce the adverse health impacts of particulate matter and exposure to toxic air contaminants, it is essential that the Plan represents the needs of all stakeholders. For the business community this means that control measures must be more than just feasible, they must be reasonable, acceptable to industry, and cost effective, as measured by a standard or standards which are suitable to business.

Finally, when reading the last sentence on Page I-3: "*Another long-term study of a national cohort found that long-term exposures to ozone were associated with respiratory-related causes of mortality,* ***but not cardiovascular causes, when PM2.5 exposure were also included in the analysis,***" we believe there is a conflict with a statement made on Page I-10, halfway down the page beginning with the sentence: "*The major types of effects associated with particulate matter include:*

- *Increased mortality*
- *Exacerbation of respiratory disease* ***and of cardiovascular disease*** *as evidenced by increases in:*
    - *Respiratory symptoms*
    - *Hospital admissions and emergency room visits*
    - *Physician office visits*
    - *School absences*
    - *Work loss days*
- *Effects on lung function*
- *Changes in lung morphology*

Legitimate scientific research - regardless of the point of view - should be part of the collaborative process between the district and relevant stakeholders, if we are to create a better consensus on how to improve air quality as required by existing law while simultaneously improving the region's economy.

In closing, I want to express my sincere appreciation for inviting me to serve on the AQMP Advisory Group and on the AQMD Advisory Council, and thank you for the opportunity to comment on this important Appendix to the 2012 AQMP.

Yours very truly,

Bill La Marr
Executive Director
California Small Business Alliance

From: Julia Lester [mailto:JLester@environcorp.com]
Sent: Wednesday, July 11, 2012 9:36 PM
To: Jean Ospital
Subject: Great meeting today!

Jean,

At our meeting today, I promised to send you two things tonight. Here you go:

- Latest MSAT list
  - Reference: http://www.fhwa.dot.gov/environment/air_quality/air_toxics/policy_and_guidance/100109guidmem.pdf
  - From the document:
    "EPA identified seven compounds with significant contributions from mobile sources that are among the national and regional-scale cancer risk drivers from their 1999 National Air Toxics Assessment (NATA) (http://www.epa.gov/ttn/atw/nata1999/). These are *acrolein, benzene, 1,3-butidiene, diesel particulate matter plus diesel exhaust organic gases (diesel PM), formaldehyde, naphthalene, and polycyclic organic matter*."
- EPA figure on progression of new standards
  - I'm still checking my citations for the presentation I remember. I will have to send it later.

I thought that the discussion at the meeting today was very thought provoking. As I mentioned, I thought that the draft Appendix I did a nice job describing and summarizing the latest pertinent health studies (by pollutant).

Regards,

Julia

ENVIRON

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From:	Rob McConnell
To:	Jean Ospital
Cc:	Marilyn Traynor
Subject:	FW: Review of Health Effects - 2012 AQMP Draft Appendix I
Date:	Monday, July 09, 2012 7:28:20 AM
Attachments:	2012 AQMP Appendix I Draft 06-05-2012.pdf

Dear Dr. Ospital,

I attach the AQMP health effects appendix with a few comments embedded in the text. In general, I think this is a good summary drawing on the key studies and reviews conducted as the foundation for regulatory decisions by EPA staff and CARB.

Although there is a review of toxicity of ultrafine particles, there is no mention of the strong emerging epidemiological evidence that near-roadway exposures cause asthma and ischemic heart disease. Ultrafine particles are a leading candidate for the causal component of the near-roadway mixture. I know you have administrative constraints based on the current regulatory framework and the evidence base, and the current lack of a standard covering UF particles. However, if ultrafine particles are to be reviewed, the near-roadway literature may deserve some mention. Dr. Nino Kunzli, a world expert on the health effects of air pollution, recently published an editorial (I believe it was in the European Respiratory Journal) calling for regulation of ultrafine PM fraction.

Hope this is useful. Will there be a full AQMP that we will be asked to review later or is the extent of our commitment/obligation in this regard?

As I indicated to you earlier, it's unlikely I'll be able to join you on the 11th, but I'd be happy to review any follow-up documents or comment on any discussion items that correspond to my area of expertise.

Sincerely,

Rob McConnell MD
Professor of Preventive Medicine.
Keck School of Medicine
University of Southern California

The major subgroups of the population considered to be at increased risk from ozone exposure are outdoor exercising individuals, including children, and people with preexisting respiratory disease(s) such as asthma. The data base identifying the former group as being at increased risk to ozone exposure is much stronger and more quantitative than that for the latter group, probably because of a larger number of studies conducted with healthy individuals. The adverse effects reported with short-term ozone exposure are greater with increased activity because activity increases the breathing rate and the volume of air reaching the lungs, resulting in an increased amount of ozone reaching the lungs. Children may be a particularly vulnerable population to air pollution effects because they spend more time outdoors, are generally more active, and have a higher ventilation rate than adults.

A number of adverse health effects associated with ambient ozone levels have been identified from laboratory and epidemiological studies (EPA, 1996; 2006, 2011; ATS, 1996). These include increased respiratory symptoms, damage to cells of the respiratory tract, decrease in lung function, increased susceptibility to respiratory infection, and increased risk of hospitalization.

Increases in ozone levels are associated with elevated absences from school. The Children's Health Study, conducted by researchers at the University of Southern California, followed a cohort of children that live in 12 communities in Southern California with differing levels of air pollution for several years. A publication from this study reported that school absences in fourth graders for respiratory illnesses were associated with ambient ozone levels. An increase of 20 ppb ozone was associated with an 83% increase in illness-related absence rates (Gilliland, 2001).

The number of hospital admissions and emergency room visits for all respiratory causes (infections, respiratory failure, chronic bronchitis, etc.) including asthma shows a consistent increase as ambient ozone levels increase in a community. These excess hospital admissions and emergency room visits are observed when hourly ozone concentrations are as low as 0.06 to 0.10 ppm.

Numerous recent studies have found positive associations between increases in ozone levels and excess risk of mortality. These associations persist even when other variables including season and levels of particulate matter are accounted for. This indicates that ozone mortality effects may be independent of other pollutants (Bell, 2004).

Multicity studies of short-term ozone exposures (days) and mortality have also examined regional differences. Evidence was provided that there were generally higher ozone-mortality risk estimates in northeastern U.S. cities, with the southwest and urban mid-west cities showing lower or no associations (Smith, 2009; Bell, 2008). Another long-term study of a national cohort found that long-term exposures to ozone were associated with respiratory-related causes of mortality, but not

Summary of Comments on 2012 AQMP Appendix I Draft 06-05-2012.pdf

Page: 11

Author: rmcconne Subject: Sticky Note Date: 7/10/2012 10:54:29 AM

Not mutually exclusive. I think the exercising asthmatic children are one of the more studied at risk groups. Exercise in non-asthma causing new onset depends largely on our study, which has gotten a lot of attention because design was strong.

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

Smaller particles can also be inhaled deep into the lungs. As much as 50% of 0.02 µm diameter particles are estimated to be deposited in the alveolar region of the lung. There is complex nature of the relation between deposition and particle size. The ultrafine particles generally have higher fractional deposition in the alveolar region. However, for the smaller nucleation mode (particles less than 0.01 µm size) the deposition in the alveolar region declines, but increases in the extrathoracic region.

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

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, 2011, for example found exposure to diesel exhaust particulate attenuated both acetylcholine and sodium-nitroprusside -induced vasorelaxation.

There are no long-term studies of human population exposure to ultrafine particle, as there is a lack of a monitoring network in the U.S. There have been several cross sectional epidemiological studies of ultrafine particles, mainly from Europe. Some of these studies found effects on hospital admissions, emergency department visits, for respiratory and cardiovascular effects. Other studies, however, have not found such effects (EPA, 2009). Concentrations of ultrafine particles can vary geographically, and it is not clear how well central site monitors may capture actual exposures.

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 (EPA, 2009). These are depicted in the table below.

Page: 27

Author: rmcconne Subject: Sticky Note Date: 7/10/2012 10:54:29 AM
spelled Araujo

Author: rmcconne Subject: Sticky Note Date: 7/10/2012 10:54:29 AM
I think most have been time series studies rather than cross sectional, but you might check to be sure.

The Children's Health Study in Southern California found associations of air pollution, including NO_2, PM10, and PM2.5, with respiratory symptoms in asthmatics (McConnell, 1999). Particles and NO_2 were correlated, and effects of individual pollutants could not be discerned. A subsequent analysis indicated a stronger role for NO_2 (McConnell, 2002).

Ambient levels of NO_2 were also associated with a decrease in lung function growth in a group of children followed for eight years. In addition to NO_2, the decreased growth was also associated with particulate matter and airborne acids. The study authors postulated that these may be a measure of a package of pollutants from traffic sources. (Gauderman, 2004).

Results from controlled exposure studies of asthmatics demonstrate an increase in the tendency of airways to contract in response to a chemical stimulus (bronchial reactivity). Effects were observed with exposures from 0.1 to 0.3 ppm NO_2 for periods ranging from 30 minutes to 3 hours. A similar response is reported in some studies with healthy subjects at higher levels of exposure (1.5 - 2.0 ppm). Mixed results have been reported when people with chronic obstructive lung disease are exposed to low levels of NO_2.

Short-term controlled studies of animals exposed to NO_2 over a period of several hours indicate cellular changes associated with allergic and inflammatory response and interference with detoxification processes in the liver. In some animal studies the severity of the lung structural damage observed after relatively high levels of short-term ozone exposure is observed to increase when animals are exposed to a combination of ozone and NO_2.

In animals, longer-term (3-6 months) repeated exposures at 0.25 ppm appear to decrease one of the essential cell-types (T-cells) of the immune system. Non-specific changes in cells involved in maintaining immune functions (cytotoxic T-cells and natural killer cells) have been observed in humans after repeated exposure (4-6 days) to >0.6 ppm of NO_2 (20 min. - 2 hours). All these changes collectively support the observation reported both in population and animal studies of increased susceptibility to infections, as a result of NO_2 exposure.

The U.S. EPA recently adopted a new short-term standard of 100 ppb (0.1 ppm) averaged over 1 hour. The standard was designed to protect against increases in airway reactivity in individuals with asthma observed in controlled exposure studies, as well as respiratory symptoms observed in epidemiological studies.

SULFUR DIOXIDE

Controlled laboratory studies involving human volunteers have clearly identified asthmatics as the most 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.

Page: 31

Author: rmcconne Subject: Sticky Note Date: 7/10/2012 10:54:29 AM
You don't draw conclusion but implies something stronger than what I think the results actually support...

Jean Ospital

From: Wayne Miller [wayne@cert.ucr.edu]
Sent: Wednesday, July 11, 2012 11:06 AM
To: Jean Ospital
Cc: Marilyn Traynor
Subject: RE: Advisory Council meeting at 2:00 p.m. on July 11, 2012 @ SCAQMD in CC-8 re: Review of Health Effects-2012 AQMP Draft Appendix I
Attachments: June 2012 IARC.pdf

Jean .. Nice work and addition for the AQMP. My two suggestions focus on the PM section.

First, while PM is a criteria pollutant and part of NAAQS, the introduction should mention that it is legally a Toxic Air Contaminant California and
words along CARB's introductory language for diesel PM might be appropriate.

Background on Diesel Health Effects (http://www.arb.ca.gov/research/diesel/diesel-health.htm)

Diesel engines emit a complex mixture of air pollutants, composed of gaseous and solid material. The visible emissions in diesel exhaust are known as particulate matter or PM. In 1998, California identified diesel exhaust particulate matter (PM) as a toxic air contaminant based on its potential to cause cancer, premature death, and other health problems. Diesel engines also contribute to California's fine particulate matter (PM2.5) air quality problems. Those most vulnerable are children whose lungs are still developing and the elderly who may have other serious health problems. Based on year 2006-2008 emissions in California, diesel PM contributes each year to approximately 2,000 premature deaths, with an uncertainty range of 1,500 to 2,400.

Second, while their report came out after your report, it would be valuable to add the recent finding of IRAC: " as of June 12, 2012 " the International Agency for Research on Cancer (IARC), which is part of the World Health Organization (WHO), today classified diesel engine exhaust as carcinogenic to humans (Group 1), based on sufficient evidence that exposure is associated with an increased risk for lung cancer." The press release is attached ..

Respectfully submitted, Wayne Miller,PhD

International Agency for Research on Cancer

World Health Organization

PRESS RELEASE
N° 213

12 June 2012

IARC: DIESEL ENGINE EXHAUST CARCINOGENIC

Lyon, France, June 12, 2012 -- After a week-long meeting of international experts, the International Agency for Research on Cancer (IARC), which is part of the World Health Organization (WHO), today classified diesel engine exhaust as **carcinogenic to humans (Group 1)**, based on sufficient evidence that exposure is associated with an increased risk for lung cancer.

Background
In 1988, IARC classified diesel exhaust as *probably carcinogenic to humans (Group 2A)*. An Advisory Group which reviews and recommends future priorities for the IARC Monographs Program had recommended diesel exhaust as a high priority for re-evaluation since 1998.

There has been mounting concern about the cancer-causing potential of diesel exhaust, particularly based on findings in epidemiological studies of workers exposed in various settings. This was re-emphasized by the publication in March 2012 of the results of a large US National Cancer Institute/National Institute for Occupational Safety and Health study of occupational exposure to such emissions in underground miners, which showed an increased risk of death from lung cancer in exposed workers (1).

Evaluation
The scientific evidence was reviewed thoroughly by the Working Group and overall it was concluded that there was *sufficient evidence* in humans for the carcinogenicity of diesel exhaust. The Working Group found that diesel exhaust is a cause of lung cancer (*sufficient evidence*) and also noted a positive association (*limited evidence*) with an increased risk of bladder cancer (Group 1).

The Working Group concluded that gasoline exhaust was possibly carcinogenic to humans (Group 2B), a finding unchanged from the previous evaluation in 1989.

Public health
Large populations are exposed to diesel exhaust in everyday life, whether through their occupation or through the ambient air. People are exposed not only to motor vehicle exhausts but also to exhausts from other diesel engines, including from other modes of transport (e.g. diesel trains and ships) and from power generators.

Given the Working Group's rigorous, independent assessment of the science, governments and other decision-makers have a valuable evidence-base on which to consider environmental standards for diesel exhaust emissions and to continue to work with the engine and fuel manufacturers towards those goals.

Increasing environmental concerns over the past two decades have resulted in regulatory action in North America, Europe and elsewhere with successively tighter emission standards for both diesel and gasoline engines. There is a strong interplay between standards and technology – standards drive technology and new technology enables more stringent standards. For diesel engines, this required changes in the fuel such as marked decreases in sulfur content, changes in engine design to burn diesel fuel more efficiently and reductions in emissions through exhaust control technology.

However, while the amount of particulates and chemicals are reduced with these changes, it is not yet clear how the quantitative and qualitative changes may translate into altered health effects; research into

IARC: Diesel engines exhaust carcinogenic

this question is needed. In addition, existing fuels and vehicles without these modifications will take many years to be replaced, particularly in less developed countries, where regulatory measures are currently also less stringent. It is notable that many parts of the developing world lack regulatory standards, and data on the occurrence and impact of diesel exhaust are limited.

Conclusions
Dr Christopher Portier, Chairman of the IARC working Group, stated that "The scientific evidence was compelling and the Working Group's conclusion was unanimous: diesel engine exhaust causes lung cancer in humans." Dr Portier continued: "Given the additional health impacts from diesel particulates, exposure to this mixture of chemicals should be reduced worldwide."(2)

Dr Kurt Straif, Head of the IARC Monographs Program, indicated that "The main studies that led to this conclusion were in highly exposed workers. However, we have learned from other carcinogens, such as radon, that initial studies showing a risk in heavily exposed occupational groups were followed by positive findings for the general population. Therefore actions to reduce exposures should encompass workers and the general population."

Dr Christopher Wild, Director, IARC, said that "while IARC's remit is to establish the evidence-base for regulatory decisions at national and international level, today's conclusion sends a strong signal that public health action is warranted. This emphasis is needed globally, including among the more vulnerable populations in developing countries where new technology and protective measures may otherwise take many years to be adopted."

Summary evaluation
The summary of the evaluation will appear in The Lancet Oncology as an online publication ahead of print on June 15, 2012.

(1) JNCI J Natl Cancer Inst (2012) doi:10.1093/jnci/djs034
http://jnci.oxfordjournals.org/content/early/2012/03/05/jnci.djs034.abstract; and
JNCI J Natl Cancer Inst (2012) doi: 10.1093/jnci/djs035
http://jnci.oxfordjournals.org/content/early/2012/03/05/jnci.djs035.abstract

(2) Dr Portier is Director of the National Center for Environmental Health and the Agency for Toxic Substances and Disease Registry at the Centers for Disease Control and Prevention (USA).

For more information, please contact
Dr Kurt Straif, **IARC Monographs Section**, at +33 472 738 507, or **straifk@iarc.fr**;
Dr Lamia Tallaa, **IARC Monographs Section**, at +33 472 738 385, or **tallaal@iarc.fr**;
Nicolas Gaudin, **IARC Communications Group**, at +33 472 738 478, or **com@iarc.fr;**
Fadela Chaib, WHO News Team, at +41 79 475 55 56, or **chaibf@who.int.**

Link to the **audio file** posted shortly after the media briefing:
http://terrance.who.int/mediacentre/audio/press_briefings/

About IARC
The International Agency for Research on Cancer (IARC) is part of the World Health Organization. Its mission is to coordinate and conduct research on the causes of human cancer, the mechanisms of carcinogenesis, and to develop scientific strategies for cancer control. The Agency is involved in both epidemiological and laboratory research and disseminates scientific information through publications, meetings, courses, and fellowships.

IARC: Diesel engines exhaust carcinogenic

Annexes

Evaluation groups - Definitions

Group 1: *The agent is carcinogenic to humans*.
This category is used when there is *sufficient evidence of carcinogenicity* in humans. Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than *sufficient* but there is *sufficient evidence of carcinogenicity* in experimental animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity.

Group 2.
This category includes agents for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost *sufficient*, as well as those for which, at the other extreme, there are no human data but for which there is evidence of carcinogenicity in experimental animals. Agents are assigned to either Group 2A (*probably carcinogenic to humans*) or Group 2B (*possibly carcinogenic to humans*) on the basis of epidemiological and experimental evidence of carcinogenicity and mechanistic and other relevant data. The terms *probably carcinogenic* and *possibly carcinogenic* have no quantitative significance and are used simply as descriptors of different levels of evidence of human carcinogenicity, with *probably carcinogenic* signifying a higher level of evidence than *possibly carcinogenic*.

- **Group 2A:** The agent is *probably carcinogenic to humans*.
  This category is used when there is *limited evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals. In some cases, an agent may be classified in this category when there is *inadequate evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent may be classified in this category solely on the basis of *limited evidence of carcinogenicity* in humans. An agent may be assigned to this category if it clearly belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified in Group 1 or Group 2A.

- **Group 2B:** The agent is *possibly carcinogenic to humans*.
  This category is used for agents for which there is *limited evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals. It may also be used when there is *inadequate evidence of carcinogenicity* in humans but there is *sufficient evidence of carcinogenicity* in experimental animals. In some instances, an agent for which there is *inadequate evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals together with supporting evidence from mechanistic and other relevant data may be placed in this group. An agent may be classified in this category solely on the basis of strong evidence from mechanistic and other relevant data.

Group 3: The agent is *not classifiable as to its carcinogenicity to humans*.
This category is used most commonly for agents for which the evidence of carcinogenicity is *inadequate* in humans and *inadequate* or *limited* in experimental animals.
Exceptionally, agents for which the evidence of carcinogenicity is *inadequate* in humans but *sufficient* in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans.
Agents that do not fall into any other group are also placed in this category.

An evaluation in Group 3 is not a determination of non-carcinogenicity or overall safety. It often means that further research is needed, especially when exposures are widespread or the cancer data are consistent with differing interpretations.

IARC, 150 Cours Albert Thomas, 69372 Lyon CEDEX 08, France - Tel: +33 (0)4 72 73 84 85 - Fax: +33 (0)4 72 73 85 75

IARC: Diesel engines exhaust carcinogenic

Group 4: The agent is *probably not carcinogenic to humans*.
This category is used for agents for which there is *evidence suggesting lack of carcinogenicity* in humans and in experimental animals. In some instances, agents for which there is *inadequate evidence of carcinogenicity* in humans but *evidence suggesting lack of carcinogenicity* in experimental animals, consistently and strongly supported by a broad range of mechanistic and other relevant data, may be classified in this group.

Evidence for studies in humans - Definition

As shown previously, the evidence relevant to carcinogenicity is evaluated using standard terms. For studies in humans, evidence is defined into one of the following categories:

Sufficient evidence of carcinogenicity: The Working Group considers that a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence. A statement that there is *sufficient evidence* is followed by a separate sentence that identifies the target organ(s) or tissue(s) where an increased risk of cancer was observed in humans. Identification of a specific target organ or tissue does not preclude the possibility that the agent may cause cancer at other sites.

Limited evidence of carcinogenicity: A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

Inadequate evidence of carcinogenicity: The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer, or no data on cancer in humans are available.

Evidence suggesting lack of carcinogenicity: There are several adequate studies covering the full range of levels of exposure that humans are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent and any studied cancer at any observed level of exposure. The results from these studies alone or combined should have narrow confidence intervals with an upper limit close to the null value (e.g. a relative risk of 1.0). Bias and confounding should be ruled out with reasonable confidence, and the studies should have an adequate length of follow-up. A conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the cancer sites, conditions and levels of exposure, and length of observation covered by the available studies. In addition, the possibility of a very small risk at the levels of exposure studied can never be excluded.

In some instances, the above categories may be used to classify the degree of evidence related to carcinogenicity in specific organs or tissues.

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From: Soret, Samuel (LLU) [mailto:ssoret@llu.edu]
Sent: Wednesday, July 11, 2012 9:12 PM
To: Jean Ospital
Subject: Appendix I: comments and articles

Jean:

Per our conversation during this afternoon's meeting, I am enclosing the mentioned articles:

1) Two studies provide new evidence that prenatal exposure to PAHs, at levels commonly encountered in New York City (and other urban areas), is associated with obesity in childhood (Rundle et al., 2012) and may adversely affect child behavior (anxiety, depression and attention problems; Perera et al., 2012).

Rundle et al. Association of Childhood Obesity With Maternal Exposure to Ambient Air Polycyclic Aromatic Hydrocarbons During Pregnancy. *Am J Epidemiol*. 2012 Jun 1;175(11):1163-72.

Perera et al. Prenatal Polycyclic Aromatic Hydrocarbon (PAH) Exposure and Child Behavior at Age 6-7 Years. *Environ Health Perspect*. 2012 Jun;120(6):921-6.

2) According to a recent investigation by Loma Linda University scientists (Spencer-Hwang et al., 2011), for kidney transplant recipients, ambient ozone levels potentially are associated with higher risk of fatal CHD. For each 10-ppb increase in O3, risk of fatal coronary heart disease increased by 34% (95% confidence interval, 3%-76%) in models adjusted for sex, race, age, year of transplant, primary cause of kidney failure, months of pre-transplant dialysis, and PM10. Please note that the publication of this article was accompanied by an invited editorial (see attached pdf: "Laden editorial") on the same issue of the *American Journal of Kidney Diseases* by Francine Laden (Harvard School of Public Health) and Wolfgang Winkelmayer (Stanford University School of Medicine). While numerous studies exist on the effects of air pollution on health-related outcomes in the general population or certain subpopulations, this is the first study in patients with kidney disease. As pointed out by Laden, the overarching question is whether kidney transplant recipients (and possibly other organ recipients) should be considered a susceptible subpopulation in the context of the Clean Air Act. These patients experience states of increased inflammation and oxidative stress, which may make enhance their susceptibility to air pollution. In addition, transplant patients receive long-term immunosuppressive medication. Immunosuppression per se may increase subsequent health risks among these patients.

Spencer-Hwang et al. Ambient air pollutants and risk of fatal coronary heart disease among kidney transplant recipients. *Am J Kidney Dis*. 2011 Oct;58(4):608-16.

Best.

Sam

Sam Soret, PhD, MPH —*Chair, Department of Environmental Health & Geoinformatics Sciences*
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From: Froines, John [jfroines@ucla.edu]
Sent: Monday, August 06, 2012 2:49 PM
To: Marilyn Traynor; Afif El-Hasan (Afif.h.el-hasan@bp.org); Afif El-Hasan (afifhaitham@yahoo.com); Bill LaMarr (BillLaMarr@msn.com); David Czamanske (dczamanske@hotmail.com); Ed Laird (elaird@coatingsresource.com); Emily Nelson (dremilynelson@gmail.com); makeoverearth.com, gary; Greg Adams (gadams@lacsd.org); Lester, Julia; wang, Michael; Mike Wang (mwang@wspa.org); radtech.org, rita; Rob McConnell (rmcconne@hsc.usc.edu); Rob McConnell (rmcconne@usc.edu); 'Soret, Samuel (LLU)'; Todd Campbell (tcampbell@cleanenergyfuels.com); Walter Siembab (ws@siembab.com); Wayne Miller (wayne.miller@ucr.edu); Wayne Miller (wayne@cert.ucr.edu)
Cc: Jean Ospital; Barbara Baird; Patti Anderson; Batteate, Christina
Subject: RE: The Advisory Council re: AQMP's Appendix I: comments and articles--Articles from Dr. Soret

To all: I have read the articles that were attached from Marilyn Traynor, and I feel it is important to comment on the PAH issue. There appears to be some belief that PAHs are the etiologic agents associated with increased health risk. However, the true etiologic agents are either epoxides, radical cations, or quinones, that is, products of metabolism or atmospheric chemistry. We have published research demonstrating that naphthalene and phenanthrene decreases as one goes east in the LA Basin whereas the levels of quinones increases as one travels from Santa Monica/Long Beach to Riverside.
The quinones are highly reactive and likely the key agents in the toxicity of PAHs. PAHs are surrogates, but there are important issues about the levels of PAHs in relation to PAH quinones. The research on PAHs is well meaning, but there needs to be a better understanding of the chemistry that results in toxicity. This is quite important. Our research at the Long Beach Railyard showed the highest PAHs, but the inflammatory markers were off the charts in San Bernadino. It makes a difference whether the key agents are properly understood. See Trevor Penning et al, Chemical Research in Toxicology, volume 12(1), 1999 and the myriad of papers that followed to the present. I hope this is of interest. The key in all this is that the primary etiologic agents from fossil fuels are prooxidant (ROS) pathways or binding with electrophilic agents. PAHs themselves require bioactivation or atmospheric chemistry to act toxicologically.
John Froines

From: Marilyn Traynor [mailto:MTraynor@aqmd.gov]
Sent: Thursday, August 02, 2012 10:22 AM
To: Afif El-Hasan (Afif.h.el-hasan@bp.org); Afif El-Hasan (afifhaitham@yahoo.com); Bill LaMarr (BillLaMarr@msn.com); David Czamanske (dczamanske@hotmail.com); Ed Laird (elaird@coatingsresource.com); Emily Nelson (dremilynelson@gmail.com); makeoverearth.com, gary; Greg Adams (gadams@lacsd.org); Froines, John; Lester, Julia; wang, Michael; Mike Wang (mwang@wspa.org); radtech.org, rita; Rob McConnell (rmcconne@hsc.usc.edu); Rob McConnell (rmcconne@usc.edu); 'Soret, Samuel (LLU)'; Todd Campbell (tcampbell@cleanenergyfuels.com); Walter Siembab (ws@siembab.com); Wayne Miller (wayne.miller@ucr.edu); Wayne Miller (wayne@cert.ucr.edu)
Cc: Jean Ospital; Barbara Baird; Patti Anderson
Subject: To: The Advisory Council re: AQMP's Appendix I: comments and articles--Articles from Dr. Soret

TO: The Advisory Council
RE: AQMP Appendix I-Health Effects

This message is sent by Marilyn Traynor on behalf of Jean Ospital, Health Effects Officer, SCAQMD
Attached are the studies that Dr. Soret discussed at the Advisory Council meeting on July 11, 2012.

Marilyn Traynor
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From: Soret, Samuel (LLU) [mailto:ssoret@llu.edu]
Sent: Wednesday, July 11, 2012 9:12 PM
To: Jean Ospital
Subject: Appendix I: comments and articles

Jean:

Per our conversation during this afternoon's meeting, I am enclosing the mentioned articles:

1) Two studies provide new evidence that prenatal exposure to PAHs, at levels commonly encountered in New York City (and other urban areas), is associated with obesity in childhood (Rundle et al., 2012) and may adversely affect child behavior (anxiety, depression and attention problems; Perera et al., 2012).

Rundle et al. Association of Childhood Obesity With Maternal Exposure to Ambient Air Polycyclic Aromatic Hydrocarbons During Pregnancy. *Am J Epidemiol*. 2012 Jun 1;175(11):1163-72.

Perera et al. Prenatal Polycyclic Aromatic Hydrocarbon (PAH) Exposure and Child Behavior at Age 6-7 Years. *Environ Health Perspect*. 2012 Jun;120(6):921-6.

2) According to a recent investigation by Loma Linda University scientists (Spencer-Hwang et al., 2011), for kidney transplant recipients, ambient ozone levels potentially are associated with higher risk of fatal CHD. For each 10-ppb increase in O3, risk of fatal coronary heart disease increased by 34% (95% confidence interval, 3%-76%) in models adjusted for sex, race, age, year of transplant, primary cause of kidney failure, months of pre-transplant dialysis, and PM10. Please note that the publication of this article was accompanied by an invited editorial (see attached pdf: "Laden editorial") on the same issue of the *American Journal of Kidney Diseases* by Francine Laden (Harvard School of Public Health) and Wolfgang Winkelmayer (Stanford University School of Medicine). While numerous studies exist on the effects of air pollution on health-related outcomes in the general population or certain subpopulations, this is the first study in patients with kidney disease. As pointed out by Laden, the overarching question is whether kidney transplant recipients (and possibly other organ recipients) should be considered a susceptible subpopulation in the context of the Clean Air Act. These patients experience states of increased inflammation and oxidative stress, which may make enhance their susceptibility to air pollution. In addition, transplant patients receive long-term immunosuppressive medication. Immunosuppression per se may increase subsequent health risks among these patients.

Spencer-Hwang et al. Ambient air pollutants and risk of fatal coronary heart disease among kidney transplant recipients. *Am J Kidney Dis*. 2011 Oct;58(4):608-16.

Best.

Sam

Sam Soret, PhD, MPH —*Chair, Department of Environmental Health & Geoinformatics Sciences*
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From: Emily Nelson
To: Jean Ospital
Cc: John J. Benoit
Subject: AQMP Appendix I comments
Date: Friday, August 31, 2012 12:33:28 PM

Hello Jean,

Thank you for the opportunity to participate in the SCAQMD Advisory Council with focus on health effects of PM10. I believe your summary of Health Effects of Air Pollution included as Appendix I of the Draft 2012 AQMP is a thorough and comprehensive update on the latest published scientific research.

The discussion at our Advisory Council meeting on July 11, 2012 was excellent. After a review of the Draft published in July, I am confident that you included our substantive comments within the scope of purpose for Appendix I. As new and ongoing research in conducted, it clarifies the mechanisms of the health effects and drives the regulatory standard review process.

It is exciting progress to have the Multiple Air Toxics Exposure Study IV include a year of ultrafine particulate monitoring at ten stations as well as near sources. For personal reasons, it would be rewarding to have the MATES from 1987 included in your references!

I look forward to reviewing your Draft Final in early September.

Sincerely,
Emily Nelson, D.Env.

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Marilyn Traynor

From: Marilyn Traynor
Sent: Wednesday, October 03, 2012 1:48 PM
To: Marilyn Traynor
Subject: FW: synthesis paper
Attachments: EHP-117-167.pdf

From: Froines, John [mailto:jfroines@ucla.edu]
Sent: Monday, September 17, 2012 9:10 AM
To: Jean Ospital
Cc: Batteate, Christina
Subject: FW: synthesis paper

Jean: Please use the attached as my contribution to the AQMP. One paper reflects Particle Center work up to 2009 and the second paper represents work to the present and it is in press. The two papers reflect the overview of the Particle Center efforts and are comphrehensive in nature. These papers are the most advanced documents on the topic of airborne particulate matter including ultrafines. Note that the papers represent my thinking as I am an author on both and was very actively involved in their preparation. You will see references to our work in the papers. The authors in the second paper (most recent) include two distinguished epidemiologists, Jonathan Samet and Ralph Delfino. As you know Ralph is a member of our Center and his work has been funded by AQMD. These papers represent the most advanced work in the field. You should use the papers as my comments since I am an author and they reflect my knowledge base.

Rob McConnell should review the epidemiology that is directly pertinent to issues in California including work by Burt Brunekreef on the mortality issues. I am not an epidemiologist and Rob would be the more appropriate person, since he can discuss the work of Jerrett, Enstrom, and Brunekreef. In addition AQMD is currently funding Dr. Art Cho on mechanistic issues relating to particles and vapors in relation to inflammation. This funded proposal reflects our mechanistic considerations.

The two EHP papers should be read and considered carefully as they represent the state of the art. The 2012 paper is in press and should not be quoted until I give the go ahead. Get back to me with questions.
John

NOTE: The first paper referenced above follows. The second paper is in press and is not included at this time. The reference follows:

[Breysse PN, Delfino RJ, Dominici F, Elder ACP, Frampton MW, Froines JR, Geyh AS, Godleski JJ, Gold DR, Hopke PK, Koutrakis P, Li N, Oberdörster G, Pinkerton KE, Samet JM, Utell MJ, Wexler AS. U.S. EPA Particulate Matter Research Centers: Summary of Research Results for 2005–2011. Air Quality, Atmosphere and Health. In Press (2012).]

A link will be provided to this document once it is published.

Particulate Matter (PM) Research Centers (1999–2005) and the Role of Interdisciplinary Center-Based Research

Elinor W. Fanning,[1] John R. Froines,[1] Mark J. Utell,[2] Morton Lippmann,[3] Gunter Oberdörster[2], Mark Frampton,[2] John Godleski,[4] and Tim V. Larson[5]

[1]Center for Environmental and Occupational Health, School of Public Health, University of California at Los Angeles, Los Angeles, California, USA; [2]University of Rochester Medical Center, Rochester, New York, USA; [3]New York University School of Medicine, New York, New York, USA; [4]Department of Environmental Health, Harvard University School of Public Health, Boston, Massachusetts, USA; [5]Department of Civil and Environmental Engineering, University of Washington, Seattle, Washington, USA

Objective: The U.S. Environmental Protection Agency funded five academic centers in 1999 to address the uncertainties in exposure, toxicity, and health effects of airborne particulate matter (PM) identified in the "Research Priorities for Airborne Particulate Matter" of the National Research Council (NRC). The centers were structured to promote interdisciplinary approaches to address research priorities of the NRC. In this report, we present selected accomplishments from the first 6 years of the PM Centers, with a focus on the advantages afforded by the interdisciplinary, center-based research approach. The review highlights advances in the area of ultrafine particles and traffic-related health effects as well as cardiovascular and respiratory effects, mechanisms, susceptibility, and PM exposure and characterization issues.

Data sources and synthesis: The collective publications of the centers served as the data source. To provide a concise synthesis of overall findings, authors representing each of the five centers identified a limited number of topic areas that serve to illustrate the key accomplishments of the PM Centers program, and a consensus statement was developed.

Conclusions: The PM Centers program has effectively applied interdisciplinary research approaches to advance PM science.

Key words: acute effects, biological mechanisms, chronic effects, criteria pollutants, dosimetry, exposure assessment, morbidity, mortality, particulate matter. *Environ Health Perspect* 117:167–174 (2009). doi:10.1289/ehp.11543 available via *http://dx.doi.org/* [Online 15 September 2008]

The U.S. Environmental Protection Agency (EPA) funded five academic centers in 1999 to address the uncertainties in exposure, toxicity and health effects of airborne particulate matter (PM) identified in the "Research Priorities for Airborne Particulate Matter" of the National Research Council (NRC 1998). Centers were established at Harvard University (Boston, MA), New York University (New York, NY), University of Rochester (Rochester, NY), University of Washington (Seattle, WA), University of California (Irvine, CA), University of California (Los Angeles, CA), and University of Southern California (Los Angeles, CA). All centers were structured to promote interdisciplinary approaches to address the research priorities of the NRC. A midterm report of PM Center findings was published previously (Lippmann et al. 2003). This report highlights selected accomplishments from the first 6 years of the PM Centers, with a focus on the advantages of interdisciplinary, center-based research. A more detailed summary of research findings and bibliography may be found in supplemental material available from the U.S. EPA PM Centers website (U.S. EPA 2008).

PM Exposure Research Highlights

Characterization of ambient PM. The PM Centers worked to characterize ambient PM and the substantial variation of concentration and composition with source, region, seasonal and diurnal patterns, and size fraction. Examples of these findings follow. In the eastern United States, $PM_{2.5}$ (PM with aerodynamic diameter < 2.5 μm) composition varies seasonally, with relatively more sulfate from long-range transport in the winter, and nitrate in the summer. Substantial spatial variability in PM components and copollutants was observed (Maciejczyk and Chen 2005). In the Pacific Northwest, organic carbon (OC) derived from wood burning is a major contributor to fine particle mass (Larson et al. 2006). PM_{10} (PM < 10 μm in aerodynamic diameter) collected in Southern California derives largely from road dust and soil and contains significant quantities of metals, whereas $PM_{2.5}$ from the same locations contains primarily nitrates, OC, and elemental carbon (EC). Ultrafine PM (UFP; PM < 0.1 μm in aerodynamic diameter) is especially high in OC (Sardar et al. 2005). Semivolatile components of PM have received increased attention in recent investigations, especially with regard to combustion-derived UFP in which a significant fraction of emissions by mass can consist of semivolatile material that has condensed onto a nonvolatile, primarily carbon core (Kuhn et al. 2005a; Robinson et al. 2007). Atmospheric processes generate UFP in regions of the Los Angeles, California, air basin that receive advected pollutant air masses (Fine et al. 2004; Singh et al. 2006). The role of atmospheric chemistry in formation of UFP is important: photooxidation of diesel emissions rapidly generates organic PM (Ntziachristos et al. 2007).

Source apportionment. Research on sources emphasized mobile sources/traffic during the first 6 years of the PM Centers (see below). A workshop was held by the PM Centers to compare different methods for source apportionment of PM. The outcomes of different analytical methods found good agreement across different investigators and methods in apportioning sources of $PM_{2.5}$ mass in two U.S. cities: Phoenix, Arizona, and Washington, D.C. (Hopke et al. 2006; Thurston et al. 2005). Center research also included identification of tracer compounds for use in identifying sources of ambient particles (Fine et al. 2004).

Personal exposure. A significant body of data on personal exposure resulted from field studies of the PM Centers, including longitudinal studies conducted in different airsheds, populations, and housing. Extensive intrapersonal and interpersonal variability in the ratio of personal to ambient exposure measures was observed in some studies (Liu et al. 2003), but taken collectively the data establish that ambient air concentrations at central site monitors can yield valid estimates of average personal exposure for population-based epidemiologic studies (Sarnat et al. 2000, 2002). The location of central site monitors, extent of PM penetration into indoor environments, personal activities, and the influence of

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Progress reports and citations to additional PM Center publications are available on the U.S. Environmental Protection Agency (U.S. EPA) Web site at http://es.epa.gov/ncer/science/pm/centers.html

The authors applaud the efforts of all PM Center researchers and the U.S. EPA for continued support of this critical research area. U.S. EPA program officers S. Katz and G. Robarge were invaluable in coordinating the preparation of this manuscript.

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The authors declare they have no competing financial interests.

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indoor PM sources can affect personal/ambient exposure ratios (Larson et al. 2004; Sarnat et al. 2006). The effects of these factors differ with PM size and composition; for example, freeway-derived UFP in the 70- to 100-nm range penetrated indoors to a greater extent than 10- to 20-nm PM (Zhu et al. 2005). The relationship of ambient criteria pollutant concentrations to ambient and personal $PM_{2.5}$ was explored. Ambient criteria pollutant levels were better predictors of personal $PM_{2.5}$ than they were of personal exposure to the gaseous species themselves, suggesting that the criteria pollutants may be useful as surrogates of $PM_{2.5}$ exposure, but are unlikely to act as confounders in epidemiologic studies (Sarnat et al. 2005). In a study of ambient UFP, hourly and 24-hr number concentrations were not significantly associated with concentrations of gaseous copollutants (Sardar et al. 2004).

PM Health Effects and Mechanisms of Injury Highlights

During the effort of the U.S. EPA to establish a national ambient air quality standard for fine particles, considerable questions about the biological plausibility of epidemiologic findings on hospitalization and mortality from cardiopulmonary effects arose. As a result the NRC committee recommended research into the mechanisms of injury that underlie PM health effects, especially daily mortality. Developments in defining toxicologic mechanisms and intermediate clinical conditions that may explain the observed cardiovascular mortality are one of the highest impact areas of the scientific contributions of the PM Centers, in particular by addressing PM size-specific research, for example, ultrafine, fine, and coarse PM.

PM effects on the cardiovascular system. The PM Centers convened a workshop to discuss potential mechanisms of PM-associated cardiovascular effects and to identify fruitful research approaches [Frampton et al. 2009 (in press; Utell et al. 2002] (Figure 1). During the first 6 years, center investigators have contributed to several review papers on cardiovascular responses to inhaled UFP and $PM_{2.5}$ (Brook et al. 2004; Delfino et al. 2005; Godleski 2006; Mar et al. 2006; Pope and Dockery 2006). New statistical methodology was developed and applied to strengthen the interpretation of acute mortality studies (Coull et al. 2001; Janes et al. 2005; Schwartz and Coull 2003; Zanobetti et al. 2000, 2001; Zeka and Schwartz 2004). Epidemiologic studies that focused on specific cardiovascular outcomes, such as myocardial infarction (Peters et al. 2001, 2004; Zanobetti and Schwartz 2005) or cause-specific mortality (Franklin et al. 2007; Miller et al. 2007; Pope et al. 2002; Zeka et al. 2005) produced hypotheses for testing in laboratory animal research and human clinical studies. Toxicologists have contributed by identifying cellular and biomolecular mechanisms involved in the cardiovascular effects that result from acute and long-term exposures to ambient PM (Araujo et al. 2008; Corey et al. 2006; Lippmann et al. 2005a, 2006; Sun et al. 2005). Most recently, toxicologic studies (Ghelfi et al. 2008) have shown that increases in reactive oxygen species (ROS) in the heart associated with inhalation of concentrated ambient particles (CAPs) may be abrogated by blocking neural receptors in the lung (Figure 2).

Investigations in the PM Centers and elsewhere supported the hypothesis that inflammatory responses contribute to cardiovascular toxicity. Possible mechanisms were proposed. Pulmonary inflammation could release ROS, cytokines, and chemokines from the lung to the systemic circulation (Frampton et al. 2006b). Vascular inflammatory markers were associated with $PM_{2.5}$ exposure in a subchronic mouse study (Sun et al. 2005). Gong et al. (2007), which demonstrated that both diesel extract and oxidized lipid components synergistically affect the expression profile of several gene modules related to vascular inflammatory processes. Evidence for an increase in C-reactive protein and a shift to a procoagulatory state of the blood was seen in coronary artery disease patients exposed to various size fractions of PM (Rückerl et al. 2006). Temporal and other parameters differed with the specific air pollution mixture in this study, which limited interpretation. Pope et al. (2004) concluded that fine particulate air pollution is a risk for cause-specific cardiovascular disease mortality via inflammation, accelerated atherosclerosis, and altered autonomic function. Zeka et al. (2006) reached similar conclusions. Their epidemiologic study supports the hypothesis that particles can induce cardiovascular disease through inflammatory pathways and suggests greater toxicity of traffic-related particles.

Autonomic function effects manifested as alterations in heart rate and heart rate variability (HRV) have been associated with $PM_{2.5}$ exposure. Decreased HRV was associated with

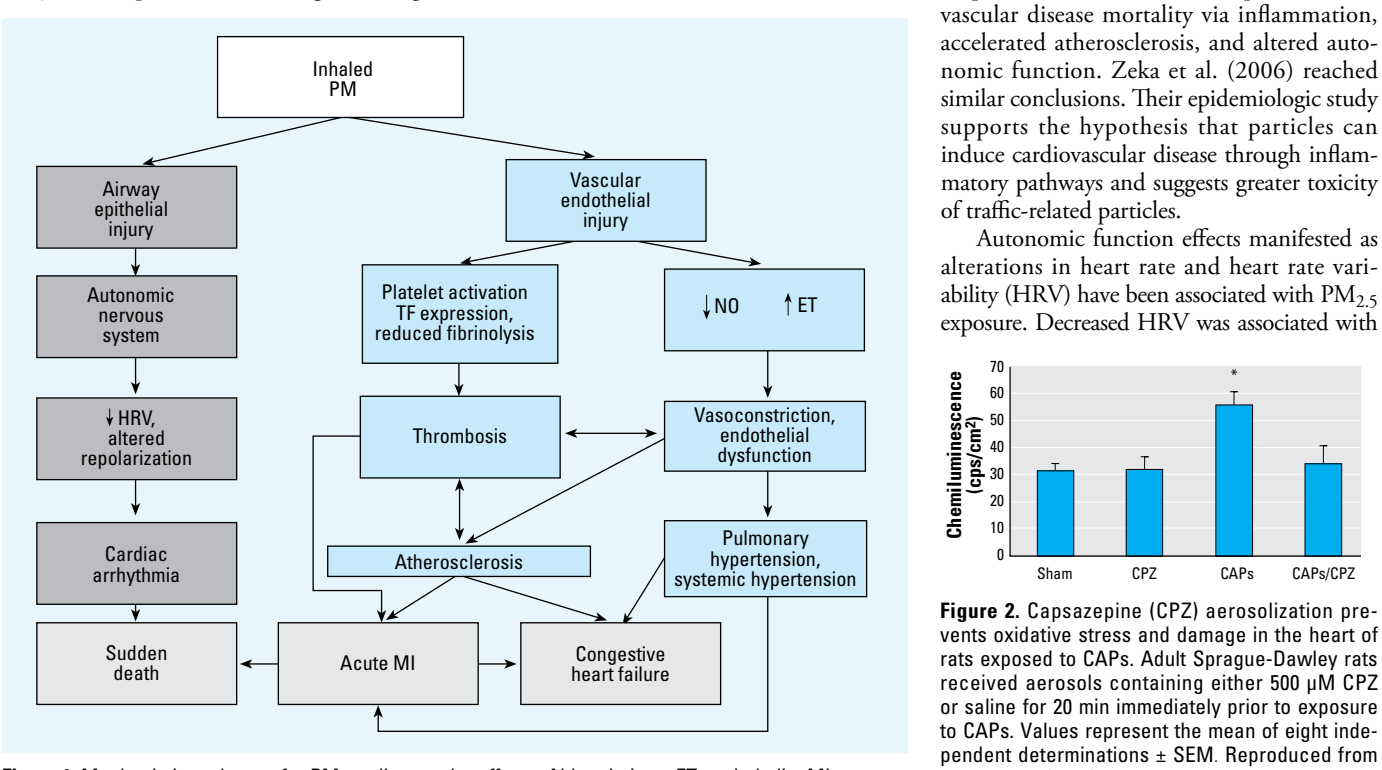

Figure 1. Mechanistic pathways for PM cardiovascular effects. Abbreviations: ET, endothelin; MI, myocardial infarction; NO, nitric oxide; TF, tissue factor. Modified from Frampton et al. 2009 (in press) with permission from Wolters Kluwer.

Figure 2. Capsazepine (CPZ) aerosolization prevents oxidative stress and damage in the heart of rats exposed to CAPs. Adult Sprague-Dawley rats received aerosols containing either 500 μM CPZ or saline for 20 min immediately prior to exposure to CAPs. Values represent the mean of eight independent determinations ± SEM. Reproduced from Ghelfi et al. (2008) with permission from Society of Toxicology.
*$p < 0.05$.

$PM_{2.5}$ exposure in panel studies of elderly subjects (Adar et al. 2007; Henneberger et al. 2005; Schwartz et al. 2005a). No associations with altered heart rate or HRV were seen in Seattle during the winter woodburning season (Mar et al. 2005b; Sullivan et al. 2005). A population-based study that drew on an established cohort (the Normative Aging Study) confirmed the association between decreased HRV and $PM_{2.5}$ seen in other studies; history of ischemic heart disease, hypertension, and diabetes modified the effects of $PM_{2.5}$ (Park et al. 2005). Cardiac arrhythmias and vascular changes such as endothelial cell responses and alterations in blood pressure are other important clinical signs of cardiovascular toxicity that have been identified in both humans and animals exposed to PM (Frampton et al. 2006b; Gong et al. 2004; Nadziejko et al. 2002).

Atherosclerosis is emerging as an important toxic end point of $PM_{2.5}$ exposure. Atherosclerosis findings may be related to reports of myocardial infarction associated with $PM_{2.5}$ in epidemiologic studies (Peters et al. 2004; Zanobetti and Schwartz 2005). The Peters study relates traffic exposures and myocardial infarction. Atherosclerotic lesions in a susceptible mouse model were enhanced by $PM_{2.5}$ exposure in a number of reports (Araujo et al. 2008; Chen and Hwang 2005; Chen and Nadziejko 2005; Lippmann et al. 2005b; Sun et al. 2005). Araujo et al. (2008) compared the proatherogenic effects of ambient UFP with $PM_{2.5}$ in apolipoprotein E–deficient mice. UFP-exposed mice exhibited significantly larger atherosclerotic lesions than mice exposed to $PM_{2.5}$ or filtered air (Figure 3).

Respiratory effects of PM exposure. PM Centers research has added to a wide body of literature investigating toxicologic mechanisms and effects of PM in the respiratory system. Overall, the issue of respiratory effects and PM exposure has been reviewed recently with reference to work produced by the PM Centers as well as others (Boothe and Shendell 2008; Salam et al. 2008). Salam focuses on asthma, whereas the Boothe and Shendell paper addresses some other end points in addition to respiratory effects. Results from clinical and panel studies in asthmatic and elderly subjects, as well as experimental studies in animals and *in vitro* cellular systems with relevance to respiratory tissues were reported. The discovery that UFP deposition is increased in asthmatic subjects during exercise has important implications for defining populations at greater risk of PM-related effects (Chalupa et al. 2004; Daigle et al. 2003). Adjuvant effects of ambient PM in promoting allergic airways responses occurred in a sensitized mouse model (Kleinman et al. 2005). Acute exposures to ambient PM in Seattle were associated with increased inflammation in asthmatic subjects, as measured by exhaled nitric oxide (Jansen et al. 2005; Koenig et al. 2005; Mar et al. 2005a). Respiratory effects in children were also a focus. Increased risk of infant hospitalization for bronchiolitis was significantly associated with subchronic and chronic exposures to PM in Los Angeles (Karr et al. 2007), where exposures in the month prior to hospitalization (subchronic) and mean lifetime exposure (chronic) referenced to the case diagnosis date were assessed on the basis of data derived from the California Air Resources Board. Epidemiologic studies that linked the PM Centers and the Children's Health Study (CHS) contributed findings that identify infants and children as important populations of concern for respiratory effects of PM (Gauderman et al. 2004, 2005, 2007; Molitor et al. 2007; Trenga et al. 2006). These studies demonstrate that exposure to $PM_{2.5}$ and other air pollutants were associated with reduced lung function growth in children and provided evidence for compromised lung function. The CHS/PM Center studies identified traffic as a risk factor (Gauderman et al. 2004, 2005, 2007; McConnell et al. 2006).

Identification of new target tissues. UFP of carbon-13 were detected in the olfactory bulbs of rats after inhalation exposure (Oberdörster et al. 2004), suggesting that the central nervous system is a potentially important toxicologic target of $PM_{2.5}$ (Figure 4). In support of this significant result, studies of mice chronically exposed to ambient $PM_{2.5}$ documented loss of brain neurons (Veronesi et al. 2005) and changes in gene expression in the brain consistent with inflammatory effects (Gunnison and Chen 2005). In another study, proinflammatory cytokines were increased in brains of mice exposed to concentrated $PM_{2.5}$ compared with those of control animals (Campbell et al. 2005).

Chemical mechanisms of PM toxicity. To better identify the most toxic PM components and sources, the PM Centers have pursued experimental linkages between toxicologic properties and specific physical/chemical characteristics of particles including size, surface area, and PM components such as transition metals, endotoxin, and organics including reactive organic compounds. Multiple chemical and biological mechanisms by which PM can induce toxic effects in a variety of target cell types have been proposed (Frampton 2006; Yang et al. 2008). Oxidative stress, a common effect of toxicant exposure, is a change in the redox environment of the cell (Schafer and Buettner 2001) through changes in the ratios of concentrations of oxidized to reduced cellular antioxidants. Oxidative stress occurs by increasing intracellular ROS or by depleting glutathione (GSH). GSH is the predominant antioxidant in cells and plays important roles in protecting against oxidative and electrophile stress (Rahman and MacNee 2000). A number of PM Center studies during the first 6 years contributed to what is now a strong evidentiary basis for oxidative damage as a general toxicologic mechanism of PM injury (Delfino et al. 2005; Ghelfi et al. 2008; González-Flecha 2004; Gurgueira et al. 2002; Li et al. 2003a, 2003b; Rhoden et al. 2004, 2005; Tao et al. 2003; Xia et al. 2006). There is widespread agreement throughout the PM Centers that oxidative stress may be a mechanism of major importance for cardiorespiratory effects.

Studies of reactive chemical components of ambient PM samples reported that particles possess intrinsic chemical reactivity

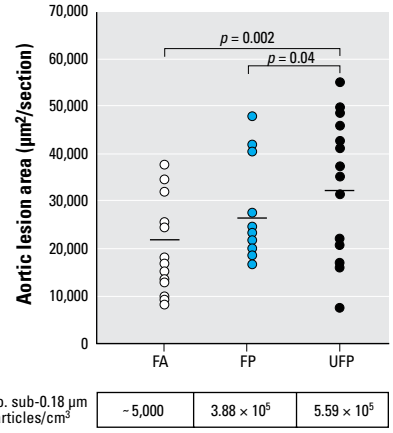

Figure 3. UFP is the most proatherogenic fraction. Atherosclerotic lesions were quantitatively analyzed in serial aortic root sections and stained with oil red O. Lesional area was scored as square micrometers per section and averaged ≥ 25 sections per animal. Group averages are indicated by straight horizontal bars. One mouse exposed to filtered air (FA) was an obvious outlier in its group and was removed from the atherosclerotic lesion analysis. However, its inclusion did not modify the overall significance. Mice exposed to FA are represented by white circles (n = 14), fine particles (FP) by blue circles (n = 16), and UFPs by black circles (n = 15). Reproduced from Araujo et al. (2008) with permission from Wolters Kluwer.

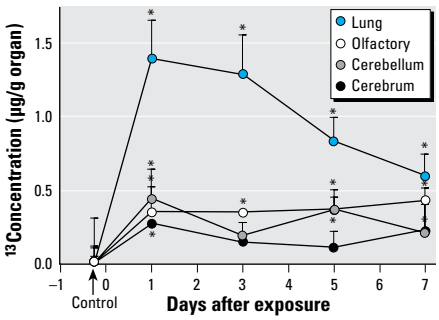

Figure 4. Time course of ^{13}C tissue concentrations in lung, olfactory bulb, cerebrum, and cerebellum of rats after a 6-hr inhalation exposure to ultrafine (36 nm count median diameter) elemental ^{13}C particles (n = 3 rats per time point). Adapted from Oberdörster et al. (2004) with permission from Taylor and Francis.
*$p < 0.05$ (ANOVA).

that may play an important role in toxicity (Cho et al. 2005; Venkatachari et al. 2005). Covalent modification of biological molecules by reactive electrophilic compounds, particularly organics, and ROS production are two key chemical mechanisms by which PM can disrupt intracellular biochemistry, ultimately altering gene expression and subcellular organelle function in target cells. Center investigators demonstrated covalent binding of a cellular enzyme by electrophilic agents, including organic compounds, present in ambient PM (Rodriguez et al. 2005; Samet et al. 1999) and reported that PM can directly inhibit the activity of enzymes involved in oxidative stress response in a cell-free assay (Hatzis et al. 2006). There is accumulating evidence that transition metals such as copper, vanadium, chromium, nickel, cobalt, and iron, as well as aromatic and polar organic substances, play a role in ROS production. An important role of metals may be alteration of signal transduction pathways involving oxidative stress (Samet et al. 2003). Assays that can screen for both oxidative and covalent binding properties of PM are of interest for comparing the toxicologic potential of PM from different sources, locations of interest, season, and other parameters of interest (Borm et al. 2007).

Life shortening associated with exposure to PM. In analyses at the Harvard Center in which daily deaths in 10 European cities were investigated by examining all-cause, respiratory, and cardiovascular deaths for all ages and stratifying by age groups, it was found that the effect of air pollution is not limited to advancing mortality by a few weeks, but that effects persist for over a month after exposure. The short-term mortality effect size estimate for PM_{10} doubles when longer-term effects for all mortality and cardiovascular mortality are considered and becomes five times higher for respiratory mortality (Zanobetti et al. 2003). Reduction of ambient air pollution levels was associated with reduced total, cardiovascular, and lung cancer mortality in the Harvard Six Cities Cohort (Laden et al. 2006). Long-term exposure was associated with excess lung cancer in cohort studies of Pope et al. (2002), Laden et al. (2006), and Pope and Dockery (2006).

Susceptibility factors and populations of concern for PM-induced health effects. When the PM Centers research was initiated, epidemiologic studies had indicated that the elderly and people with cardiovascular or chronic lung disease were at greater risk for morbidity and mortality associated with acute PM exposure. The PM Centers explored the basis for this susceptibility and also produced research findings that expand the spectrum of populations of concern. Support for the epidemiologic observations that elderly and chronic obstructive pulmonary disease patients have higher rates of hospitalization and mortality associated with acute PM exposure has come from human clinical studies showing that elderly people experience greater effects of PM on HRV and blood parameters (Park et al. 2005; Pope and Dockery 2006; Schwartz et al. 2005a, 2005b). Further support for the elderly as a population of concern comes from studies of geriatric laboratory animals (Elder et al. 2004a, 2004b).

A study of PM-related daily mortality found greater effects in diabetic subjects (Zeka et al. 2006). The increase in mortality in diabetics may be related to increased susceptibility to the cardiovascular effects of PM exposure, as indicated by greater rate of hospitalization for heart disease (Zanobetti and Schwartz 2002), sensitivity to changes in HRV (Park et al. 2005), and altered vasomotor function (O'Neill et al. 2005) in diabetic subjects. It is possible that these patients may be more susceptible to inflammatory effects of PM, which in turn affect vascular tissues (O'Neill et al. 2007). In contrast, recent results from the Women's Health Initiative suggest that diabetics in this cohort were not at increased risk (Miller et al. 2007). More work on this subject is needed, and controlled human exposures in diabetic studies have been initiated by the PM Centers (Frampton et al. 2006a). Schwartz et al. (2005b) reported an association between presence or absence of the allele for glutathione-*S*-transferase M1 and the high frequency component of HRV. Genetic susceptibility is an area in which the PM Centers are currently increasing research focus.

Advances in Critical Interdisciplinary Research Areas

Interdisciplinary research has been a hallmark of the PM Centers since their inception. Two subject areas that were exemplary in terms of bringing together multiple investigative perspectives were investigations of UFP and mobile sources.

Ultrafine particles: unique in composition and toxicity. Center-based research allowed a major effort to characterize size distributions, chemical speciation, and the effect of atmospheric processes of UFP to be integrated with toxicologic research (Donaldson and Stone 2003). UFP in urban airsheds are largely derived from fresh combustion sources, although secondary formation of UFP from atmospheric photochemical processes is also an important source (Sioutas et al. 2005). UFP freshly generated by combustion are short-lived and subsequently grow to form aggregates. UFP dominate particle number concentration in ambient PM samples while contributing little to PM mass concentrations. In part because of a complex fractal structure (Friedlander and Xiong 2000), UFP possess much greater surface area per unit mass than larger ambient particles. The large surface area, in turn, allows greater per-mass concentrations of adsorbed or condensed toxic air pollutants (oxidant gases, organic compounds, transition metals) to collect on UFP (Sioutas et al. 2005). Studies on ambient and model particles have concluded that the large specific surface area of UFP may be a key component in their toxicology (Oberdörster 2001).

The PM Centers produced an integrated body of exposure and toxicologic studies on ambient and model UFP as well as studies of controlled human exposures. Dosimetry work showed that UFP will have significant accumulation in the lung (Kreyling et al. 2006). In addition, UFP of varying composition can cross cellular membranes by diffusion (Geiser et al. 2005) and gain access to vulnerable targets within cells. The potential for translocation from the site of lung deposition into systemic circulation, although rates have been low with test particles (Kreyling et al. 2002), could have major mechanistic implications (Elder and Oberdörster 2006). Electron microscopy indicated subcellular penetration and mitochondrial damage by UFP in *in vivo* studies and, to a lesser extent, by fine particles (Li et al. 2003b). Disruption of mitochondrial functions may play an important role in PM-mediated health effects (Xia et al. 2007).

In a study of size-segregated concentrated ambient PM samples, the ability of PM to catalyze ROS generation, an initial step in the induction of oxidative stress, was greatest in the UFP fraction (Cho et al. 2005). Li et al. (2003a) summarized contrasting features of coarse, fine, and ultrafine particles from Southern California, including relevant chemical and biological parameters. The toxicologic findings correlated with PM OC and polycyclic aromatic hydrocarbon (PAH) composition, suggesting a role of organic agents in generating redox activity (Table 1).

The PM Centers conducted controlled human exposure studies with UFP. Results from these studies were limited, because of small group sizes and because these exposures are necessarily brief and conducted at low concentrations compared with the background PM exposures that may be experienced by urban study subjects. In the first set of studies, short-term exposures were conducted with 10–50 $\mu g/m^3$ carbon UFP generated in the laboratory. Alterations in blood cell adhesion molecules and in a marker of vascular perfusion suggest that UFP exposure may produce subtle changes in pulmonary vasoconstriction (Frampton 2007; Pietropaoli et al. 2004). A small but statistically significant reduction in arterial oxygen saturation and some evidence for reduced HRV were found, although the small study size limited interpretation (Gong et al. 2008). An expanded focus on UFP in epidemiologic studies is needed but has been limited to date by the challenges of assessing exposure to UFP.

Traffic: mobile sources are highly relevant to the public health impacts of PM. The center-based research context was particularly useful in advancing the science on mobile sources of PM, the focus of an extensive international research effort. Numerous investigations of the physical and chemical attributes of PM collected alongside freeways and in roadway tunnels were performed. The results have yielded data on size distribution, number and mass concentrations, chemical speciation, emissions factors, volatility, penetration indoors, and the impact of atmospheric processes on roadway PM (Biswas et al. 2007; Fine et al. 2004; Geller et al. 2006; Kuhn et al. 2005b, 2005c; Phuleria et al. 2007; Sardar et al. 2005; Zhu et al. 2005). Detailed spatial profiles of UFP concentration at varying distances from freeways were generated (Zhu et al. 2002a, 2002b). Concentrations of UFP drop exponentially with distance from the center of the freeway, reaching upwind levels at approximately 300 meters. The size distribution of UFP also changed markedly with distance reflective of coagulation and other atmospheric particle processes. Winter particle number concentrations are greater than summer, indicating formation of UFP from vapor condensation. Exposure to motor vehicle exhaust emissions during commuting may constitute a substantial fraction of daily personal PM exposure, especially to UFP (Sioutas et al. 2005; Zhu et al. 2007).

Toxicologic studies of traffic-derived aerosols studied by PM Centers included *in vitro* findings that implicate PM collected in freeway microenvironments in the production of reactive chemical species, stimulation of proinflammatory effects, and altered gene expression in cellular test systems. UFP fraction, carbonaceous content, and an organic tracer for vehicles were linked with toxicologic activity of PM in a variety of assays (Cho et al. 2005; Li et al. 2003a, 2003b). Several studies of laboratory animals exposed to PM on or near busy roadways have identified cardiovascular and allergic airways effects (Elder et al. 2004b, 2007; Kleinman et al. 2005). Evidence that traffic-derived air pollution affects humans has expanded significantly during the first 6 years of PM Centers funding, implicating mobile source in respiratory effects in children (Gauderman et al. 2004, 2005, 2007; McConnell et al. 2006), cardiovascular effects (Riediker et al. 2004) including myocardial infarction (Peters et al. 2004; Tonne et al. 2007), and low birth weight (Wilhelm and Ritz 2003). Toxicologic studies are needed to follow up the epidemiologic findings of effects on the fetus. In a reanalysis of data from the Harvard Six Cities study of daily mortality and PM, source apportionment approaches identified the mobile source factor as most strongly associated with increased daily mortality (Laden et al. 2000).

Policy Implications of PM Centers Research

Research findings from the PM Centers have had a significant influence on science policy, most directly in terms of the science that underlies the National Ambient Air Quality Standards (NAAQS) for PM. The findings of morbidity and mortality that form the scientific basis for the short-term and annual PM NAAQS were strengthened through epidemiologic and statistical research. Mechanistic investigations and studies of preclinical markers established biological plausibility for observed relationships between ambient air PM and observed acute mortality. In personal exposure studies, validation of the use of central site ambient concentrations provided crucial support to the interpretation of epidemiologic results.

The PM NAAQS are based on mass concentration. The state of the science suggests that no single parameter, whether mass, size fraction, surface area, or a particular chemical component, is responsible for all the diverse mechanisms and toxicologic end points that have been associated with PM, and a more sophisticated approach to standards will be needed. Based on findings from the PM Centers and others, the potential efficacy of number and component based standards should be assessed. As more data become available to link specific PM emissions sources, chemical composition, and physical characteristics with quantitative measures of toxicity, the question of source-specific control strategies to maximize public health protection also needs to be considered.

The increasing level of evidence that UFP are toxic but may not be controlled well by existing regulatory approaches raises other policy issues including mitigation of the risk of health effects associated with housing, schools, parks, and other heavily populated public facilities located near heavily traveled roadways, busy seaports, and other combustion sources that are the major urban sources of exposure to UFP. There are potential environmental justice concerns associated with transportation-derived combustion, as it is often areas of lower socioeconomic status that are most affected by proximity to these sources.

Looking Forward: Research Priorities and Current Directions

As the PM Centers program moved forward into the second phase, the original guiding research priorities were reevaluated, and new priorities have emerged. Several areas of investigation identified during the development of the 1997 PM NAAQS are still of critical relevance today, but the scientific questions being asked have been refined. Some research topics being pursued in the current round of PM Centers are described below.

Particle source characterization and PM components as factors in PM toxicity. The PM Centers current research agenda includes detailed studies of the physical and chemical attributes of ambient PM associated with specific sources. The current science indicates that multiple mechanisms of injury, in backgrounds modified by host susceptibility factors, can be activated by a variety of PM components and characteristics. To address the complexity associated with assessing the health effects associated with specific PM components, the current PM Centers research agenda compares toxicologic properties of PM by source type in addition to compositional attributes. Mobile sources continue to be a priority focus, and there is a need to better understand the fate of fossil fuel combustion emissions from a variety of mobile and stationary sources, including airports, seaports, and other sources as well as roadways. Building upon the productive body of work on mobile source PM in the first 6 years of PM Center work, the current PM Centers include human panel and clinical studies and toxicologic studies in laboratory animals and *in vitro* systems that test hypotheses about the effects of mobile source PM exposures. Source apportionment efforts are ongoing as well, to build on previous work that found mobile sources are dominant contributors to urban UFP loads. *In vitro* studies will pay particular attention to UFP, organic compounds, and transition metals. UFP formed from nucleation of ambient air vapors are a new focus, as they may be especially toxic.

Dosimetry and toxicokinetics. Research at the PM Centers is addressing particle deposition, uptake, distribution, and fate, including

Table 1. Contrasting features of coarse, fine, and ultrafine particles.

Parameters	Coarse PM_{10}	Fine PM_{10}	Ultrafine PM_{10}
Size (μm)	2.5–10	2.5–0.15	< 0.15
OC content	+	++	+++
EC content	+	++	+++
Metals (% of total elements)	+++	++	+
PAH content	+	+	+++
Redox activity (DTT assay)	+	++	+++
HO-1 induction	+	++	+++
GSH depletion	+	+++	+++
Mitochondrial damage	None	Some	Extensive

Data from Li et al. (2003a).

the effects of developmental stage on disposition of PM. Cell culture systems with gene expression and proteomics methods are being used for studies of metabolic and genetic responses that will be useful for toxicokinetics. Studies of the dosimetry and toxicokinetics associated with UFP are especially important, given previous PM Centers findings that these particles distribute into systemic circulation and secondary target organs such as the CNS, and can enter cells and subcellular organelles.

Mechanisms. All the current PM Centers have a strong focus on continuing to develop understanding of the toxic mechanisms that underlie clinically and epidemiologically defined adverse health effects of PM. Mechanisms being pursued include reactive chemical species that cause cellular oxidative stress responses. In the first 6 years, studies of oxidative damage associated with PM were performed using diverse chemical species, cell culture experiments, and laboratory animal studies. Evolving from that work, the current PM Centers studies are looking at markers of oxidative stress processes in humans and a range of clinical and preclinical biomarkers. The list of gene products that can be used as indicators of PM exposure or toxicity in various cell types has expanded. Mechanistic hypotheses are being tested in panel and other epidemiologic studies.

Susceptibility. Susceptibility is a major theme, drawing on the work from the earlier center and noncenter investigators showing that individuals with pulmonary and cardiac health conditions, elderly, children, diabetics, and others may be more susceptible to the adverse effects of PM exposure than the general population. The PM Centers are looking at early life exposures to PM in animal models, performing panel studies of elderly subjects or subjects with compromised health status, using a large established cohort to identify how risk factors for PM-related health outcomes may be modified by individual factors such as medication use, diet, and genotype. Compromised animal models are a key theme of current research into susceptibility. PM exposure studies on ApoE$^{-/-}$ mice (an atherosclerosis-prone model), hypertensive rats, and diabetic rats are all planned or underway.

Conclusions

In 1998, a committee of the NRC published the first of a four-volume report titled "Research Priorities for Airborne Particulate Matter" that identified the 10 highest-priority targets for PM research (NRC 1998). Within the research portfolio of the PM Centers, the priority areas have been addressed. A subsequent NRC report (2001) emphasized that these research priorities require multidisciplinary approaches. Recognizing that progress in understanding the health effects consequent to air pollution exposure requires talents from highly divergent fields, we believe that the PM Centers effectively promote interdisciplinary cross-fertilization. The next 5 years of this program will bring the experience and results of the first centers to fruition in new, focused studies that we hope will be instrumental in addressing the difficult scientific and public health policy problems that arise from ubiquitous particulate air pollution.

Correction

In the title of the manuscript originally published online, the date range in the title was incorrect. It has been corrected here.

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ATTACHMENT 4

EXTERNAL REVIEWERS' COMMENTS

Appendix I-Health Effects was submitted to the following individuals for review and comment:

Dr. Jonathan M. Samet, M.D., M.S
University of Southern California
Department of Preventive Medicine
USC Institute for Global Health

Dr. Michael Kleinman, Ph.D., M.S.
University of California, Irvine
Department of Medicine/Occupational and Environmental Medicine

Copies of their comments follow.

Keck School of Medicine of USC

Department of Preventive Medicine
Jonathan M. Samet, MD, MS
Professor and Flora L. Thornton Chair
Director, USC Institute of Global Health

September 25, 2012

Jean Ospital, MPH, PhD
Health Effects Officer
South Coast Air Quality Management District
21865 Copley Drive
Diamond Bar, CA 91765

Dear Jean,

As you requested, I attach comments concerning the Health Effects Appendix of the District's draft Air Quality Management Plan. Please do not hesitate to contact me if you have questions with regard to these comments.

Yours sincerely,

Jonathan M. Samet, MD, MS
Professor and Flora L. Thornton Chair
Department of Preventive Medicine
Director, USC Institute for Global Health

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Review: Health Effects Appendix
South Coast Air Quality Management District
Jonathan M. Samet, MD, MS

General Comments:

This relatively brief document provides an overview of the health effects of various air pollutants, giving emphasis to pollution by airborne particulate matter. The document also covers other "criteria pollutants" as well as ultrafine particulate matter and toxic air contaminants. This range of topics is appropriate to the development of an Air Quality Management Plan.

As presented, the document represents a summary, and an apparent updating of an earlier report. It is necessarily selective in its coverage and relies to an extent on the review documents prepared by the US Environmental Protection Agency for the "criteria" pollutants. I have the following general comments:

- Preparation of reviews of the health effects of air pollution is a daunting task, given the extensive data available and its continuing and rapid accrual. The South Coast Air Quality Management District is not well positioned to prepare a comprehensive and up-to-date review. Consequently, there are deficiencies of this review related to its scope and timeliness. The basis for the document's development is provided in the last paragraph on page I-2. While the statement is clear, the methods are not fully transparent. In particular, several older reviews are mentioned, along with more recent documents from the US Environmental Protection Agency and several prepared by the California EPA. I suggest that more careful attention be given to describing the basis for this review and to consideration of its methodology. For example, given the complexity and scope of the literature, the developers of the review might rely solely on summary documents or to also summarize documents and research published based on studies in California. In the present version, I could not readily identify why particular studies were included.

- I understand that the South Coast Air Quality Management District is required to provide a review in support of its air quality management plan. As stated, the California Health and Safety Code Section 40471(b) requires the preparation of 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 revisions." This document does not directly address the health impacts, if some quantification of burden is implicit in the requirement. The identification of health effects and selected of examples of risks from the literature represents a starting point in estimating the health impact. As noted in my next comment, the review might have establishing the relevance of the broad body of evidence to the South Coast Air Quality Management District as one objective.

- There is an extensive literature on airborne particulate matter and health, as well as on the risks of various other air pollutants. One question that might be reasonably addressed in this report is the generalizability of findings from this broad literature to California. Here, a careful review of studies in California might be of benefit. Additionally, considerations might be given to the mixture of pollutants in the South Coast Air Basin to support conclusions about the generalizability of findings.

- The document needs further editing in part to improve clarity and in part to bring in some of the most recent and relevant references. Additionally, if the most recent US EPA documents are to be used as the basis of the report, some updating is needed.

Specific comments:

See attached.

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 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 revisions. This document, which was prepared to satisfy that requirement, also includes the effects of the other major pollutants.

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 (morbidity) and increases in death rates (mortality).

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

- ~~Increased~~ Premature mortality
- Increased health care utilization (hospitalization, physician and emergency room visits)
- Increased respiratory illness (symptoms, infections, and asthma exacerbation) and other morbidity
- Decreased lung function (breathing capacity)
- Lung inflammation
- Potential immunological changes
- Increased airway reactivity to a known ~~chemical~~ 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.

The evidence linking these effects to air pollutants is derived from population-based observational and field studies (epidemiological) as well as controlled laboratory studies involving human subjects and animals. There have been an increasing number of studies focusing on the mechanisms (that is, on learning how specific organs, cell types, and biochemicals 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 ~~mostly~~ pollutant-specific. This is appropriate, in that different pollutants usually 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, may sometimes act together to harm health more than they would acting separately. Nevertheless, as a practical matter, health scientists, as well as regulatory officials, usually must deal with one pollutant at a time in determining health effects and 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 toxic exposure 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 document.

This summary is drawn substantially from reviews presented previously (SCAQMD, 1996, 2003, 2007), and from reviews on the effects of air pollution by the American Thoracic Society (ATS, 1996), the U.S. EPA reviews for ozone (U.S. EPA, 2006), Carbon Monoxide (U.S. EPA, 2010), and Particulate Matter (U.S. EPA, 2004, 2009), from a published review of the health effects of air pollution (Brunekreef and Holgate, 2002), and from reviews prepared by the California EPA Office of the Environmental Health Hazard Assessment for Particulate Matter (Cal EPA, 2002) and for Ozone (Cal EPA, 2005). Additional materials are from EPA's current review of the ozone standard and health effects (EPA, 2011). More detailed citations and discussions on air pollution health effects can be found in these references.[1]

[1] Most of the studies referred to in this appendix are cited in the above sources. Only more recent specific references will be cited in this summary.

OZONE

Ozone is a highly reactive compound, and is 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, it can penetrate into the gas exchange region of the deep lung.

The EPA primary standard for ozone, adopted in 2008, is 0.075 ppm averaged over eight hours. The California Air Resources Board (CARB) has established standards of 0.09 ppm averaged over one hour and at 0.070 ppm averaged over eight hours.

see later + ISA to update

The major subgroups of the population considered to be at increased risk from ozone exposure are outdoor exercising individuals, including children, and people with preexisting respiratory disease(s) such as asthma. The data base identifying the former group as being at increased risk to ozone exposure is much stronger and more quantitative than that for the latter group, probably because of a larger number of studies conducted with healthy individuals. The adverse effects reported with short-term ozone exposure are greater with increased activity because activity increases the breathing rate and the volume of air reaching the lungs, resulting in an increased amount of ozone reaching the lungs. Children may be a particularly vulnerable population to air pollution effects because they spend more time outdoors, are generally more active, and have a higher ventilation rate than adults.

A number of adverse health effects associated with ambient ozone levels have been identified from laboratory and epidemiological studies (EPA, 1996; 2006, 2011; ATS, 1996). These include increased respiratory symptoms, damage to cells of the respiratory tract, decrease in lung function, increased susceptibility to respiratory infection, and increased risk of hospitalization. mortality?

Increases in ozone levels are associated with elevated absences from school. The Children's Health Study, conducted by researchers at the University of Southern California, followed a cohort of children that live in 12 communities in Southern California with differing levels of air pollution for several years. A publication from this study reported that school absences in fourth graders for respiratory illnesses were positively associated with ambient ozone levels. An increase of 20 ppb ozone was associated with an 83% increase in illness-related absence rates (Gilliland, 2001).

The number of hospital admissions and emergency room visits for all respiratory causes (infections, respiratory failure, chronic bronchitis, etc.) including asthma

shows a consistent increase as ambient ozone levels increase in a community. These excess hospital admissions and emergency room visits are observed when hourly ozone concentrations are as low as 0.06 to 0.10 ppm.

Numerous recent studies have found positive associations between increases in ozone levels and excess risk of mortality. These associations persist even when other variables including season and levels of particulate matter are accounted for. This indicates that ozone mortality effects may be independent of other pollutants (Bell, 2004).

Multicity studies of short-term ozone exposures (days) and mortality have also examined regional differences. Evidence was provided that there were generally higher ozone-mortality risk estimates in northeastern U.S. cities, with the southwest and urban mid-west cities showing lower or no associations (Smith, 2009; Bell, 2008). Another long-term study of a national cohort found that long-term exposures to ozone were associated with respiratory-related causes of mortality, but not cardiovascular-related causes, when PM2.5 exposure were also included in the analysis.

at risk?

Several population-based studies suggest that asthmatics are more adversely affected by ambient ozone levels, as evidenced by increased hospitalizations and emergency room visits. Laboratory studies have attempted to compare the degree of lung function change seen in age and gender-matched healthy individuals versus asthmatics and those with chronic obstructive pulmonary disease. While the degree of change evidenced did not differ significantly, that finding 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 degree of change may represent a substantially greater adverse effect overall.

→ there are two issues: 1) Is asthma adversely affected by ozone? and 2) Is the lung function response to ozone different in asthmatics and non-asthmatics

Another publication from the Children's Health Study focused on children and outdoor exercise. In 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, 2002). These findings indicate that new cases of asthma in children are associated with heavy exercise in communities with high levels of ozone. While it has long been known that air pollution can exacerbate symptoms in individuals with respiratory disease, this is among the first studies that indicate ozone exposure may be causally linked to asthma onset.

associated with episodic and chronic exposure effects may not exhibit similar adaptation. That is, internal damage to the respiratory system may continue with repeated ozone exposures, even if externally observable effects (chest symptoms and reduced lung function) disappear.

In a laboratory, exposure of human subjects to low levels of ozone causes reversible decrease 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. Similar lung volume changes have also been observed in adults and children under ambient exposure conditions (0.10 - 0.15 ppm). The responses reported are indicative of decreased breathing capacity and are reversible. update with krim study?

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 recently summarized (Brown, 2008). As shown in the figure below, there is an increasing response on lung function with increasing exposure levels in moderately exercising subjects.

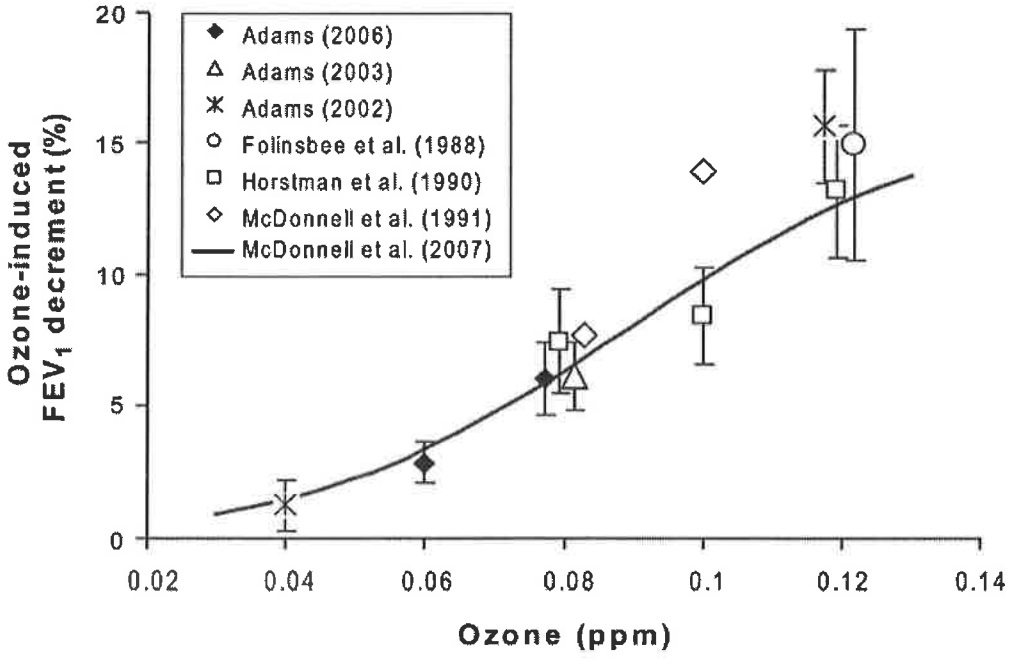

FIGURE I-1

Comparison of mean ozone-induced decrements in lung function following 6.6 hours of ozone exposure (from Brown, 2008)

In addition to controlled laboratory conditions, studies of individuals exercising outdoors, including children attending summer camp, have shown associations of reduced lung function with ozone exposure. There were wide ranges in responses among individuals.

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 (EPA, 2011).

In laboratory studies, cellular and biochemical changes associated with respiratory tract inflammation have also been consistently ~~reported~~ 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 cytokines and fibronectin. 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.

The susceptibility to ozone observed under ambient conditions could be due to the combination of pollutants that coexist in the atmosphere or ozone may actually sensitize these subgroups to the effects of other pollutants.

Some animal studies show results that indicate possible chronic effects including functional and structural changes of the lung. These changes indicate that repeated inflammation associated with ozone exposure over a lifetime may result in sufficient 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. An autopsy study involving Los Angeles County residents provided supportive evidence of lung tissue damage (structural changes) attributable to air pollution.

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 is 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. ~~Confirmation by further studies is needed.~~

In summary, adverse effects associated with ozone exposures have been well documented, although the specific causal mechanism is still somewhat unclear.

PARTICULATE MATTER

Airborne particulates are a complex group of pollutants that vary in source, size and composition, depending on location and time. 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, may also be present.

Until several years ago, the health effects of particulates were focused on those sized 10 μm (micrometers) aerodynamic diameter and smaller. These can be inhaled through the upper airways and deposited in the lower airways and gas exchange tissues in the lung. These particles are referred to as PM10. EPA initially promulgated ambient air quality standards for PM10 of 150 $\mu g/m^3$ averaged over a 24-hour period, and 50 $\mu g/m^3$ for an annual average. EPA has since rescinded the annual PM10 standard, but kept the 24-hour standard.

In recent years additional focus has been placed on particles having an aerodynamic diameter of 2.5 μm or less (PM2.5). A greater faction of particles in this size range can penetrate and deposit deep in the lungs. The EPA recently lowered the air quality standards for PM2.5 to 35 $\mu g/m^3$ for a 24-hour average and reaffirmed 15 $\mu g/m^3$ 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 EPA promulgated the initial PM2.5 standards in 1997.

Since that time, numerous studies have been published, and some of the key studies were closely scrutinized and analyses repeated. The result is that there are now substantial data confirming the adverse health effects of PM2.5 exposures. 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 larger than 2.5 μm (often referred to as the coarse fraction) 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.

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 few years. These are generally referred to as "ultrafine" particles, with diameters of 0.1 μm or less. These particles are mainly from fresh emissions of combustion sources, but are also formed in the atmosphere from photochemical reactions. Ultrafine particles have relatively short half lives (minutes to hours) and rapidly grow through condensation and coagulation process into larger particles within the PM2.5 size range. These particles are garnering interest since laboratory studies indicate that their toxicity may be higher on a mass basis than larger particles, and there is evidence that these small particles can translocate from the lung to the blood and to other organs of the body.

There have been several reviews of the health effects of ambient particulate matter (ATS, 1996; Brunekreef, 2002; U.S. EPA, 2004; U.S. EPA, 2009). 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 (Cal EPA, 2002).

The major types of effects associated with particulate matter include:

Not mentioned on page I-(

- Increased mortality
- Exacerbation of respiratory disease and of cardiovascular disease as evidenced by increases in:
    - -Respiratory symptoms
    - -Hospital admissions and emergency room visits
    - -Physician office visits
    - -School absences
    - -Work loss days
- Effects on lung function
- Changes in lung morphology

The current federal and California standards are listed below:

TABLE I-4

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 $\mu g/m^3$
PM 2.5 24-Hour Average	35 $\mu g/m^3$	--
PM 2.5 Annual Average	15 $\mu g/m^3$	12 $\mu g/m^3$

Short-Term Exposure Effects

Epidemiological studies have provided evidence for most of the effects listed above. An association between increased daily or several-day-average concentrations of PM10 and excess mortality and morbidity is consistently reported from studies involving communities across the U.S. as well as in Europe, Asia, and South America. A review and analysis of epidemiological literature for acute adverse effects was undertaken by Dockery and Pope to estimate these effects as percent increase in mortality associated with each incremental increase of PM10 by 10 $\mu g/m^3$. The estimates are presented in Table I-5. It appears that individuals who are elderly or have preexistent lung or heart disease are more susceptible than others to the adverse effects of PM10.

Many recent studies have confirmed that excess mortality and morbidity are associated with particulate matter levels. Estimates of mortality effects from these studies range from 0.3 to 1.7% increase for a 10 $\mu g/m^3$ increase in PM10 levels. The National Morbidity, Mortality, and Air Pollution Study (NMMAPS), a study of 20 of the largest U.S. cities, determined a combined risk estimate of about a 0.5% increase in total mortality for a 10 $\mu g/m^3$ increase in PM10 (Samet, 2000a). This study also analyzed the effects of gaseous co-pollutants. The results indicated that the association of PM10 and mortality were not confounded by the presence of the gaseous pollutants. When the gaseous pollutants were included in the analyses, the significance of the PM10 estimates remained. The PM10 effects were reduced somewhat when O_3 was also considered and tended to be variably decreased when NO_2, CO, and SO_2 were added to the analysis. These results argue that the effects are likely due to the particulate exposures; they cannot readily be explained by coexisting weather stresses or other pollutants.

An expansion of the NMMAPS study to 90 U.S. Cities also reported association with PM10 levels and mortality (Samet 2000b). It was discovered that this study was one that used a flawed statistical software package. The investigators have reanalyzed the data using corrected settings for the software (Dominici, 2002a, Dominici 2002b). When the estimates for the 90 cities in the study were recalculated, the estimate changed from 0.41% increase in mortality for a 10 $\mu g/m^3$ increase in PM10 to a 0.27% increase. There remained a strong positive association between acute exposure to PM10 and mortality. Thus while the quantitative estimate was reduced, the major findings of the study did not change.

TABLE I-5

Combined Effect Estimates of Daily Mean Particulate Pollution

	% CHANGE IN HEALTH INDICATOR PER EACH 10 $\mu g/m^3$ 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

severe effects, larger numbers experience milder effects, which may relate either to the coarse or to the fine fraction of airborne particulate matter.

In the NMMAPS study, hospital admissions for those 65 years or older were assessed in 14 cities. Hospital admissions for these individuals showed an increase of 6% for cardiovascular diseases and a 10% increase for respiratory disease admissions, per 50 $\mu g/m^3$ increase in PM10. The excess risk for cardiovascular disease ranges from 3-10% per 50 $\mu g/m^3$ PM10 and from 4-10% per 25 $\mu g/m^3$ PM2.5 or PM10-2.5.

Similarly, school absences, lost workdays and restricted activity days have also been used in some studies as indirect indicators of acute respiratory conditions. The results are suggestive of both immediate and delayed impact on these parameters following elevated particulate matter exposures. These observations are consistent with the hypothesis that increased susceptibility to infection follows particulate matter exposures.

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 3% to 42% for medical visits for respiratory illnesses was found corresponding to a 50 $\mu g/m^3$ change in PM10. A limited 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.

The biological mechanisms by which particulate matter can produce health effects are being investigated in laboratory studies. Inflammatory responses in the respiratory system in humans and animals exposed to concentrated ambient particles have been measured. These include effects such as increases in neutrophils in the lungs. Other changes reported include increased release of cytokines and interleukins, chemicals released as part of the inflammatory process. The effects of particulate matter may be mediated in part through the production of reactive oxygen species during the inflammatory process. Recent reviews discuss mechanistic studies in more detail (Brunekreef, 2002; Brook, 2004).

Long-Term Exposure Effects

While most studies have evaluated the acute effects, some studies specifically focused on evaluating the effects of chronic exposure to PM10 and PM2.5. Studies have analyzed the mortality of adults living in different U.S. cities. After adjusting for important risk factors, taken as a whole these studies found a positive association of deaths and exposure to particulate matter. A similar association was observable in both total number of deaths and deaths due to specific causes. The largest effects were observed from cardiovascular causes and ischemic heart disease. A shortening of lifespan was also reported in these studies.

Since the initial promulgation by EPA of the National Ambient Air Quality Standards for PM2.5, controversy has remained over the association of mortality and exposures to PM2.5. Thus an expanded discussion of these studies is presented below.

Significant associations for PM2.5 for both total mortality and cardiorespiratory mortality were reported in a study following a national cohort recruited by the American Cancer Society for a Cancer Prevention Study over several years. A re-analysis of the data from this study confirmed the initial finding (Krewski, 2000). In this study, mortality rates and PM2.5 levels were analyzed for 51 metropolitan areas of the U.S. Average levels from monitors in each area were used to estimate exposures. At these levels of aggregation, regional differences in the association of PM2.5 and mortality were noted, with higher associations in the Northeast, and lower or non-significant associations in the West.

The Harvard Six Cities Study evaluated several size ranges of particulate matter and reported significant associations with PM15, PM2.5, sulfates, and non-sulfate particles, but not with coarse particles (PM15 – PM2.5). An extension of the Harvard Six Cities Cohort confirmed the association of mortality with PM2.5 levels (Laden, 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 compounds. An update to this study covering a follow-up over the years 1974 to 2009 (Lepeule, 2012) was recently published. 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.

methods (Jerrett, 2005) and another applied land use regression techniques (Krewski, 2009) to estimate exposures to the study individuals. Significant associations of PM2.5 with mortality from all causes and cardiopulmonary disease were reported, with the magnitude of risks being up to three times higher than those from the national studies of the American Cancer Society cohort. This provides evidence that using methods to provide more detailed exposure estimates can result in stronger associations of PM2.5 and mortality.

Two recent reports have been released looking at air pollution and health effects in California. One study (Lipsett, 2011) followed school teachers recruited in 1995, and followed through 2005. Pollutant exposures at the subject residence were estimated using data from ambient monitors, and extrapolated using a distance weighted method. The authors reported significant association of PM2.5 levels and mortality from ischemic heart disease, but no associations were found with all cause, cardiovascular, or respiratory disease.

The second study (Jerrett, 2011) followed individuals in the Los Angeles area from the American Cancer Society cohort recruited starting in 1982, with follow up to 2000. Pollutant levels at subject residences were estimated using several methods. All but one of the methods found no association of all-cause mortality with PM2.5 levels. All exposure estimation methods were reported to have found significant associations with ischemic heart disease mortality, however. The authors noted that mortality rates differ in urban areas compared to non-urban areas, and so included a variable for this in a land use regression model to estimate effects on mortality. When the authors applied the land use regression model including an urban indicator to estimate exposures, all-cause mortality, mortality from cardiovascular disease, and mortality from ischemic heart disease were all significantly associated with PM2.5 levels.

Other studies report evidence indicating that particulate matter exposure early in pregnancy may be associated with lowered birth weights (Bobak, 1999). Studies from the U.S., the Czech Republic and Mexico City have reported that neonatal and early postnatal exposure to particulate matter may lead to increased infant mortality. A more recent study in Southern California found increased risks for infant deaths associated with exposures to particulates and other pollutants (Ritz, 2006). These results suggest that infants may be a subgroup affected by particulate matter exposures.

ULTRAFINE PARTICLES

As noted above, numerous studies have found association of particulate matter levels with adverse effects, including mortality, hospital admissions, and respiratory disease symptoms. The vast majority of these studies used particle mass of PM10 or PM2.5 as the measure of exposure. Some researchers have postulated, however, that ultrafine particles may be responsible for some of the observed associations of particulate matter and health outcomes (Oberdorster, et al, 1995; Seaton, et al, 1995). Ultrafine particles are ~~generally classified of 0.1 µm and small diameter.~~ have aerodynamic diameter < 0.1 µm.

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

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

Smaller particles can also be inhaled deep into the lungs. As much as 50% of 0.02 µm diameter particles are estimated to be deposited in the alveolar region of the lung. There is complex nature of the relation between deposition and particle size. The ultrafine particles generally have higher fractional deposition in the alveolar region. However, for the smaller nucleation mode (particles less than 0.01 µm size) the deposition in the alveolar region declines, but increases in the extrathoracic region.

Exposures of laboratory animals to ultrafine particles have found cardiovascular and respiratory effects. Mice exposed to concentrated near roadway ultrafine particles showed larger early atherosclerotic lesions than mice exposed to PM2.5 or filtered air (Arujo, 2008). In a mouse allergy model, exposures to concentrated ultrafine particles resulted in a greater response to antigen challenge to ovalbumin (Li, 2010), indicating that vehicular traffic exposure could exacerbate allergic inflammation in already-sensitized animals.

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, 2011, for example found exposure to diesel exhaust particulate attenuated both acetylcholine and sodium-nitroprusside -induced vasorelaxation.

NITROGEN DIOXIDE

The U.S. EPA has recently reviewed the health effects of nitrogen dioxide (U.S. EPA, 2008a). Evidence for low-level nitrogen dioxide (NO_2) exposure effects is derived from laboratory studies of asthmatics and from epidemiological studies. Additional supportive evidence is derived from animal studies.

Epidemiological studies using the presence of an unvented gas stove as a surrogate for indoor NO_2 exposures suggest an increased incidence of respiratory infections or symptoms in children. Some studies, evidence mixed.

Recent studies related to outdoor exposure have found health effects associated with ambient NO_2 levels, including respiratory symptoms, respiratory illness, decreased lung function, increased emergency room visits for asthma, and cardiopulmonary mortality. However, since NO_2 exposure generally occurs in the presence of other pollutants, such as particulate matter, these studies are often unable to determine the specific role of NO_2 in causing effects.

The Children's Health Study in Southern California found associations of air pollution, including NO_2, PM10, and PM2.5, with respiratory symptoms in asthmatics (McConnell, 1999). Particles and NO_2 were correlated, and effects of individual pollutants could not be discerned. A subsequent analysis indicated a stronger role for NO2 (McConnell, 2002).

Ambient levels of NO_2 were also associated with a decrease in lung function growth in a group of children followed for eight years. In addition to NO_2, the decreased growth was also associated with particulate matter and airborne acids. The study authors postulated that these/may be a ~~measure~~ result of a package of pollutants from traffic sources. (Gauderman, 2004). is reflect

a number of these studies have looked at consequences of inhaled allergens

Results from controlled exposure studies of asthmatics demonstrate an increase in the tendency of airways to contract in response to a chemical stimulus (bronchial reactivity). Effects were observed with exposures from 0.1 to 0.3 ppm NO_2 for periods ranging from 30 minutes to 3 hours. A similar response is reported in some studies with healthy subjects at higher levels of exposure (1.5 - 2.0 ppm). Mixed results have been reported when people with chronic obstructive lung disease are exposed to low levels of NO_2.

Short-term controlled studies of animals exposed to NO_2 over a period of several hours indicate cellular changes associated with allergic and inflammatory response and interference with detoxification processes in the liver. In some animal studies

the severity of the lung structural damage observed after relatively high levels of short-term ozone exposure is observed to increase when animals are exposed to a combination of ozone and NO_2.

In animals, longer-term (3-6 months) repeated exposures at 0.25 ppm appear to decrease one of the essential cell-types (T-cells) of the immune system. Non-specific changes in cells involved in maintaining immune functions (cytotoxic T-cells and natural killer cells) have been observed in humans after repeated exposure (4-6 days) to >0.6 ppm of NO_2 (20 min. - 2 hours). All these changes collectively support the observation reported both in population and animal studies of increased susceptibility to infections, as a result of NO_2 exposure.

The U.S. EPA recently adopted a new short-term standard of 100 ppb (0.1 ppm) averaged over 1 hour. The standard was designed to protect against increases in airway reactivity in individuals with asthma observed in controlled exposure studies, as well as respiratory symptoms observed in epidemiological studies.

SULFUR DIOXIDE

Not proven to be "most" sensitive

Controlled laboratory studies involving human volunteers have clearly identified asthmatics as ~~the most~~ 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 significant alteration of lung function, such as increases in airway resistance and decreases in breathing capacity. In some, the exposure can result in severe symptoms necessitating the use of medication for relief. The response to SO_2 inhalation is observable within 2 minutes of exposure, increases further with continuing exposure up to 5 minutes then remains relatively steady as exposure continues. SO_2 exposure is generally not associated with any delayed reactions or repetitive asthmatic attacks.

In epidemiologic studies, associations of SO_2 levels with increases in respiratory symptoms, increases in emergency department visits and hospital admissions for respiratory-related causes have been reported.

The U.S. EPA has recently revised the SO_2 air quality standard. The previous 24-hour standard was rescinded and replaced with a new 1-hour standard at 75 ppb (0.075 ppm) to protect against high short-term exposures.

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Dear Dr. Ospital:

I have completed my review of Appendix I. The comments follow.

General Comments:
The health literature in the Appendix provides valid support for the CA air quality standards. I do agree with Dr. McConnell who suggested in his comments the utility of expanding the section on epidemiological evidence showing that near roadway exposures are associated with asthma and ischemic heart disease.

With regard to air toxics it might be useful to recognize that emissions from modern diesel engines and retrofitted older diesels are quantitatively and perhaps qualitatively different from that of the older unmodified diesels which are still part of the fleet but of diminishing numbers. There is a gap in our knowledge at this time as to whether health impacts are indeed reduced (as one would expect) and better information on how long it would take to phase out unmodified diesels would be useful for future projections.

I noted a comment from Bill La Marr (California Small Business Assoc) regarding a possible conflict on I-3 and I-10. Note that I-3 deals with cardiovascular mortality studies whereas I-10 speaks to exacerbation of cardiovascular disease (i.e. morbidity) not mortality, so there is no conflict.

I also read Dr. Enstrom's comments. I considered the contention that there is "NO relationship in California between PM and total mortality". First, total mortality might not be the most useful metric to use since the most sensitive individuals include those with respiratory and cardiovascular disease. I think that Dr. Jarrett's paper using land use regression to provide improved exposure metrics demonstrate significant health effects.

I have several specific comments which are tabulated below. I also have some additional editorial suggestions that I will send by mail rather than transcribe them here.

Pg	Comment
I-2 Para 2	Although individuals inhale pollutants as a mixture under ambient conditions, the regulatory framework and the control measures developed are mostly pollutant-specific. This is appropriate, in that different pollutants usually 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, may sometimes act together to harm health more than they would acting separately. Nevertheless, evidence for more than additive effects have not been strong and, as a practical matter, health scientists, as well as regulatory officials, usually ~~must~~ deal with one pollutant at a time in ~~determining health effects and 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 toxic exposure 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 document.
I-3 Para3	Children may be a particularly vulnerable population to air pollution effects because they spend more time outdoors, are generally more active, and have a higher specific ventilation rate than adults (i.e. after normalization for body mass).
I-3 Para 5	Increases in ozone levels are associated with ~~elevated~~ increased numbers of absences from school.
I-4 Para 2	Numerous recent studies have found positive associations between increases in ozone levels and excess risk of mortality. These associations are strongest during warmer months but overall persist even when other variables including season and levels of particulate matter are accounted for. This indicates that ozone mortality effects may be independent of other pollutants (Bell, 2004).
I-4 Para 4	Since the respiration-compromised group may have lower lung function to begin with, the same total ~~degree of~~ change may represent a substantially greater relative adverse effect overall.
I-4 Para 5	Another publication from the Children's Health Study focused on children and outdoor exercise. In 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, 2002). These findings indicate that new cases of asthma in children are associated with their performance of heavy exercise in communities with high levels of ozone. While it has long been known that air pollution can exacerbate or trigger symptoms in individuals with preexisting respiratory disease, this is among the first studies that indicate ozone exposure may be causally linked to asthma onset.
I-5 Table I-1 Row1, Col 2	exposure~~, decreased temperature,~~ and other environmental factors resulting in increased summertime hospital admissions and emergency department visits for respiratory causes (NOTE: while cold air can trigger asthma, this is confusing in the face of increased effects during warmer weather) Exacerbation of respiratory symptoms (e.g., cough, chest pain) in individuals with preexisting disease (e.g., asthma) with low ambient
I-5 Table I-1 Row 2, Col2	NOTE: include reference to the latest Kim paper that shows effects at 0.06ppm Kim, C. S., N. E. Alexis, et al. (2011). "Lung function and inflammatory responses in healthy young adults exposed to 0.06 ppm ozone for 6.6 hours." American Journal of Respiratory and Critical Care Medicine **183**(9): 1215-1221. RATIONALE: Exposure to ozone causes a decrease in spirometric lung function and an increase in airway inflammation in healthy young adults at concentrations as low as 0.08 ppm, close to the National Ambient Air Quality Standard for ground level ozone. OBJECTIVES: To test whether airway effects occur below the current ozone standard and if they are more pronounced in potentially susceptible individuals, such as those deficient in the antioxidant gene glutathione S-transferase mu 1 (GSTM1). METHODS: Pulmonary function and subjective symptoms were measured in 59 healthy young adults (19-35 yr) immediately before and after exposure to 0.0 (clean air, CA) and 0.06 ppm ozone for 6.6 hours in a chamber while undergoing intermittent moderate exercise. The polymorphonuclear neutrophil (PMN) influx was measured in 24 subjects 16 to 18 hours postexposure. MEASUREMENTS AND MAIN RESULTS: Subjects experienced a significantly greater (P = 0.008) change in FEV(1) (+/- SE) immediately after exposure to 0.06 ppm ozone compared with CA (-1.71 +/- 0.50% vs. -0.002 +/- 0.46%). The decrement in FVC was also greater (P = 0.02) after ozone versus CA (-2.32 +/- 0.41% vs. -1.13 +/- 0.34%). Similarly, changes in %PMN were greater after ozone (54.0 +/- 4.6%) than CA (38.3 +/- 3.7%) exposure (P < 0.001). Symptom scores were not different between ozone versus CA. There were no significant differences in changes in FEV(1), FVC, and %PMN between subjects with GSTM1-positive and GSTM1-null genotypes. CONCLUSIONS: Exposure of healthy young adults to 0.06 ppm ozone for 6.6 hours causes a significant decrement of FEV(1) and an increase in neutrophilic inflammation in the airways. GSTM1 genotype alone appears to have no significant role in modifying the effects.
I-6 Fig I-1	Add data point from Kim (2011) O3 vs CA (-1.71 +/- 0.50% vs. -0.002 +/- 0.46%)
I-7 Para 1	One could note in Figure I-1 that, not surprisingly, the results of studies

	conducted using subjects residing in California (Adams, et. al.) are consistent with measurements made with residents of other states (e.g. Kim et al., 2011) In addition to controlled laboratory conditions, studies of individuals exercising outdoors, including children attending summer camp, have shown associations of reduced lung function with ozone exposure. There were wide ranges in responses among individuals.
I-7 Para 2	In laboratory studies, cellular and biochemical changes associated with respiratory tract inflammation have also been consistently reported 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 ~~cytokines~~ Interleukin-1, Tumor Necrosis Factor α and fibronectin.
I-7 Para 4	There may be interactions between ozone and other ambient pollutants. The susceptibility to ozone observed under ambient conditions could be modified due to the combination of pollutants that coexist in the atmosphere, or ozone ~~may actually~~might sensitize these subgroups to the effects of other pollutants.
I-7 Para 5	Some animal studies show results that indicate possible chronic effects including functional and structural changes of the lung. These changes indicate that repeated inflammation associated with ozone exposure over a lifetime may result in ~~sufficient~~ 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.
I-7 Para 7	In summary, adverse effects associated with ozone exposures have been well documented. ~~,~~ A~~a~~lthough the specific ~~causal~~ mechanisms of action are not fully identified ~~is still somewhat unclear~~there is a strong likelihood that oxidation of key enzymes and proteins and inflammatory responses play important roles.
I-8 Para 1	NOTE: It might be useful to add the following: On the basis of the most recent evaluations of ozone health effects the CASAC has recommended to the USEPA Administrator that the NAAQS be reduced and recommended a range in which 0.070 ppm would be the upper limit, i.e. moving the national standard to be consistant with the CA standard.
I-9 P 3-4	In recent years additional focus has been placed on particles having an aerodynamic diameter of 2.5 µm or less (PM2.5). A greater fraction of particles in this size range can penetrate and deposit deep in the lungs. The EPA recently lowered the air quality standards for PM2.5 to 35 µg/m3 for a 24-hour average and reaffirmed 15 µg/m3 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 EPA promulgated the initial PM2.5 standards in 1997. Since that time, numerous studies have been published, and some of the key studies were closely scrutinized and ~~analyses repeated~~the data were reanalyzed by additional investigators. The re~~sult is that there are now substantial data~~analyses ~~confirming~~ confirmed the significant findings of adverse health effects of PM2.5 exposures and some additional studies demonstrated adverse effects at ambient concentrations at or below the current NAAQS.
I-10 P 1	in the atmosphere ~~from gases~~by condensation of vapors that are emitted or by chemical or photochemical reactions with other contaminants in the air.
I-10 P 2	These particles are garnering interest since a limited number of epidemiological and several laboratory studies indicate that their toxicity may be higher on a mass basis than larger particles, and there is 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.
I-10 P 4	The major ~~types of~~ effects associated with particulate matter ~~include:~~are shown in Table I-4. California did not set a separate 24-hr average PM2.5 standard; the 35 µg/m3 NAAQS applies.
I-11 Table I-4	COMMENT: Insert NAAqS for 24 hr PM2.5 in brackets? Indicate in a footnote if the forms of the standard are not the same.
I-11 P2 L7	Was the mortality CV, Resp, total, all of the above??
I-11 P2	There are statistical associations between PM10 and several of the gaseous co-pollutants and therefore the association of PM10 and healtheffects were reduced somewhat when O_3 was also considered and tended to be variably decreased when NO_2, CO, and SO_2 were added to the analysis. However, in many studies there are significant independent associations of PM and health effects ~~These results argue~~thus supporting the contention that the effects are likely due to the particulate exposures; they cannot readily be explained by coexisting weather stresses or other pollutants.
I-13	COMMENT: It gets confusing when the basis changes from 10 µg/m3 to 25 µg/m3 or other metrics. There should be a reference for the Mexico City and Chile studies.
I-13 P3	The relative importance of both PM2.5 and PM10-2.5 may vary in different regions depending on the relative concentrations and components, which can also vary by season. A major knowledge gap is the relative paucity of direct measurements of PM2.5-10. Most estimates are made by subtracting PM2.5 from PM10 measured at co-located samplers, a process that is subject to large 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 fine (PM2.5)
I-14 P3	These observations are consistent with the hypothesis that increased susceptibility to infection follows particulate matter exposures, which is consistent with mechanistic studies that show that PM exposures suppress the innate immune system.
I-14 P 4	The findings suggest that both the fine and coarse fractions may have associations with some respiratory symptoms, consistent with mechanistic studies that both coarse and fime PM suppress innate immune functions.
I-15 P4	COMMENT: This might also be a reflection that mortality in general is lower in the western states – perhaps analogous to the "healthy worker" effect seen in occupational studies. However effects are seen more clearly when analyses are focused on susceptible groups and when more personal metrics of exposure are used as shown by Jerrit et al.
I-16 P4	COMMENT: Pollutant levels dropped dramatically from 83-02. The impact of pollution on mortality would have dropped as well. When looking at a changing independent variable it may be more appropriate to look at the changes in mortality vs the changes in pollution over the entire period rather than arbitrary slices.
I-18 P1 L4	…couple OF cohort…
I-18 P2	…fetuses and infants may be subgroups…
I-21 P2 L4	Araujo,2008
I-26 P6 L3	…have been reported. Coupled with the human clinical studies, these data suggest that SO2 can trigger asthmatic episodes in individuals with pre-existing asthma.
I-26 P7	…to protect against ~~high short term exposure~~accute asthma attacks in sensitive individuals.

Sincerely,

Michael T. Kleinman

ATTACHMENT 5

PUBLIC COMMENTS

Appendix I-Health Effects was released for public review and comment in July and September 2012.

Copies of public comments on Appendix I Health Effects follow.

Criticism of Draft 2012 South Coast Air Quality Management District Air Quality Management Plan Appendix I Health Effects

and

Request for California Health and Safety Code Section 40471 (b) Hearing on Health Impacts of Particulate Matter Air Pollution in South Coast Air Basin

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August 30, 2012

Summary of Attached Pages:

1) Enstrom Criticism of Draft 2012 AQMD AQMP Appendix I Health Effects makes the primary points that a) overwhelming epidemiologic evidence indicates particulate matter is not killing Californians; b) since 2001 AQMD has not prepared reports on "the health impacts of particulate matter in the South Coast Air Basin" in accord with California Health and Safety Code (CHSC) Section 40471 (b); c) the AQMD Advisory Council failed to properly peer review AQMP Appendix I Health Effects; and d) AQMD must hold a Governing Board Hearing on AQMP Appendix I Health Effects before the 2012 AQMP is finalized.

2) Enstrom Op-Ed for The Desert Sun on particulate matter in the Coachella Valley, which was scheduled to be published on April 4, 2012 but which has never been published, makes a strong case that a) particulate matter is not currently harming Coachella Valley residents and b) there will be no health risk from particulate matter after the Sentinal Power Plant is operational.

3) Figure 21 from 2000 Health Effects Institute Reanalysis Report by Krewski, Jerrett, et al., shows clear and large variation in PM2.5 mortality risk across the US, with low risk in California

4) Enstrom Table 1 summary of the epidemiologic evidence shows NO relationship between PM2.5 and total mortality in California.

5) Enstrom Table 2 summary of the epidemiologic evidence shows NO relationship between PM10 and total mortality in California; also, US EPA summary of PM NAAQS indicates revocation of the annual PM10 standard in 2006 due to lack of long-term health effects.

6) NCHS US map shows 2009 age-adjusted total death rate by state, with California third lowest; also, California county data shows that the death rate in the South Coast Air Basin is lower than the death rate in every state except Hawaii.

Criticism of Draft 2012 South Coast Air Quality Management District Air Quality Management Plan Appendix I Health Effects

The Southern California Air Quality Management District (AQMD) has released its Draft 2012 Air Quality Management Plan (AQMP) (http://www.aqmd.gov/aqmp/2012aqmp/index.htm). This plan proposes aggressive and costly emission control measures, such as, increased use of zero emission vehicles and severe restrictions on wood-burning fireplaces, in order to reduce air pollution in the South Coast Air Basin (SCAB). This air basin includes about 17 million residents in Orange County and the urban portions of Los Angeles, Riverside, and San Bernardino Counties. The primary goal of the AQMP is to bring the SCAB into compliance with the US Environmental Protection Agency (EPA) National Ambient Air Quality Standards (NAAQS) for criteria pollutants, such as, particulate matter (PM2.5 and PM10) and ozone. These standards are based on the nationwide health effects of these pollutants (http://www.epa.gov/air/criteria.html).

However, the AQMP needs to address the health effects of air pollution in the SCAB. In particular, California Health and Safety Code (CHSC) Section 40471 (b) specifically states "On or before December 31, 2001, and every three years thereafter, as part of the preparation of the air quality management plan revisions, the south coast district board, in conjunction with a public health organization or agency, shall prepare a report on the health impacts of particulate matter air pollution in the South Coast Air Basin. The south coast district board shall submit its report to the advisory council appointed pursuant to Section 40428 for review and comment. The advisory council shall undertake peer review concerning the report prior to its finalization and public release. The south coast district board shall hold public hearings concerning the report and the peer review, and shall append to the report any additional material or information that results from the peer review and public hearings." (http://www.leginfo.ca.gov/cgi-bin/displaycode?section=hsc&group=40001-41000&file=40460-40471).

As best I can determine, AQMD never prepared a "report on the health impacts of particulate matter air pollution in the South Coast Air Basin" at the end of 2001, 2004, 2007, or 2010. The only "health impacts" reports that I can find are Appendix I "Health Effects" of the 2003 AQMP, 2007 AQMP, and Draft 2012 AQMP. However these reports do not specifically address "the health impacts of particulate matter air pollution in the South Coast Air Basin." Indeed, the 2003 AQMP Appendix I states "The purpose of this appendix is to provide an overview of air pollution health effects, rather than to provide estimates of health risk from current ambient levels of pollutants in specific areas of the SCAB." (http://www.aqmd.gov/aqmp/docs/2003AQMP_AppI.pdf).

Failure to comply with CHSC Section 40471 (b) is a serious matter because the local health effects of PM provide the primary public health justification for the entire AQMP. Overwhelming epidemiologic evidence now indicates that there is NO relationship in California between PM and total mortality (also known as "premature deaths"), as I explained in the June 4, 2012 Orange County Register (http://www.ocregister.com/articles/air-357230-california-pollution.html).

This null relationship in California has been known since 2000, but the specific null evidence is only partially presented in the Draft 2012 AQMP and was entirely omitted from the earlier AQMPs. For instance, each AQMP Appendix I cites the 2000 Health Effects Institute Special Report "Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of Particulate Air Pollution and Mortality," a major report relied upon by EPA and AQMD. However, only the nationwide PM2.5 mortality risk results in this report are cited in the AQMP, whereas Figures 5 and 21 show substantial geographic variation in PM2.5 mortality risk across the US, with Los Angeles ranking fifth lowest among 49 cities (http://www.scientificintegrityinstitute.org/HEIFigure5093010.pdf).

In total, ten separate analyses of five major California cohorts have found no relationship between PM2.5 and total mortality. Indeed, detailed analyses of two of these cohorts, funded by AQMD and completed in 2011, have found no relationship between any criteria pollutant and total mortality in California (www.scientificintegrityinstitute.org/Enstrom081512.pdf). Keep in mind, total mortality is the primary health impact that justifies the NAAQS. However, these national standards are not based on health effects or mortality in California or the SCAB. In 2009 the SCAB had an age-adjusted total death rate lower than the death rate in every state in the continental US (http://www.scientificintegrityinstitute.org/NCHSRR070811.pdf).

The 16 members of the 2012 AQMD Advisory Council were asked on June 7, 2012 to review and comment on Appendix I, particularly regarding the "health impacts of particulate matter air pollution in the South Coast Air Basin," and to attend a July 11, 2012 meeting at AQMD regarding Appendix I. Only 7 members submitted any written comments. The three members with the most relevant scientific expertise on PM did not address the "health impacts of particulate matter air pollution in the South Coast Air Basin". UCLA Professor John R. Froines did not submit any written comments; USC Professor Rob S. McConnell did not submit any comments on PM health effects; and LLU Professor Samuel Soret failed to reveal the null PM findings from AHSMOG in the December 2011 LLU Dr. P.H. dissertation of Lie Hong Chen (http://books.google.com/books/about/Coronary_Heart_Disease_Mortality_and_Lon.html?id=pA8ltwAACAAJ).

Dr. Soret served on the committee for Dr. Chen's highly relevant dissertation, CORONARY HEART DISEASE MORTALITY AND LONG-TERM EXPOSURE TO AMBIENT PARTICULATE AIR POLLUTANTS IN ELDERLY NONSMOKING CALIFORNIA RESIDENTS. The Abstract states "The purpose of this study is to assess the effect of long-term concentrations of ambient PM on risks of all causes . . . . The health effects of long-term ambient air pollution have been studied with up to 30 years of follow-up in the AHSMOG cohort, a cohort of 6,338 nonsmoking white California adults."

Before the Draft 2012 AQMP is finalized and approved, AQMD must hold a public hearing on the health impacts of air pollution in the SCAB, in accordance with CHSC Section 40471 (b). If the hearing confirms the overwhelmingly null evidence cited above, then the AQMP should not propose emission control measures necessary to comply with NAAQS that are not appropriate for California or the SCAB. Instead, AQMD should request a waiver from compliance with the NAAQS using the special waiver status granted to California in Section 209 of the Clean Air Act (http://www.epa.gov/otaq/cafr.htm).

From: "Folmer, James" <jfolmer@palmspri.gannett.com>
To: "James E. Enstrom" <jenstrom@ucla.edu>
Date: Tue, 3 Apr 2012 09:44:35 -0700
Subject: RE: Proposed Op-Ed on Particulate Matter Health Effects in CV

Dr. Engstrom, here's the edited version. I did minimal editing, just a few tweaks to match AP style. I replaced $\mu g/m^3$ with "micrograms per cubic meter." Please let me know if that's acceptable.

Also, I took your website references out of the body of the column and put them in a breakout (below) to make it more readable.

It will be in Wednesday's edition. Thanks for the contribution.

The Desert Sun has recently published a special report and an editorial on the Sentinel power plant that is under construction by Competitive Power Ventures. Substantial concern has been expressed about the impact of the particulate matter (PM) pollution that will be generated by the plant. I would like to provide my perspective on the PM levels associated with the plant and the health effects associated with PM. PM consists of "inhalable course particles" (PM10) and "fine particles" (PM2.5).

Based on the April 15, 2010, California Energy Commission air quality assessment for the Sentinel plant, Table 13 indicates that the maximum annual background PM10 level in the Coachella Valley will be increased from 54.9 microgram per cubic meter to 55.33 during plant operation. This represents a "worse case (maximum)" increase of only 0.8 percent. Based on the South Coast Air Quality Management District (AQMD) Final 2007 Air Quality Management Plan, the maximum annual average PM10 level in the Coachella Valley (Salton Sea Air Basin) is only 45.7 micrograms per cubic meter.

All these levels are quite similar to the U.S. EPA's 1987-2006 annual standard for PM10 of 50 micrograms per cubic meter. However, this standard was revoked in 2006 due to "inadequate" evidence of long-term health effects of PM10, as summarized in the 2004 and 2009 EPA Integrated Science Assessment for Particulate Matter.
The Desert Sun claim that "the Sentinel plant would increase the (PM10) level to 277 percent above the state standard" is highly misleading because it is based on the California Energy Commission's Table 13 comparison of 55.33 micrograms per cubic meter with the California annual standard for PM10 of 20. But this state standard was established by the California Air Resources Board in 2002 and does not reflect the extensive null evidence on PM10 health effects that has been published since 2002.

In January 2007, the Air Resources Board and AQMD approved $1,034,358 in funding, half from each agency, for two major epidemiologic studies on the relationship between PM (PM10 and PM2.5) and death in California. The study based on the American Cancer Society cohort was conducted by UC Berkeley professor Michael Jerrett and 13 other investigators.

The study based on the California Teachers Study cohort was conducted by Michael Lipsett of the California Department of Public Health and nine other investigators. A primary purpose of these studies was to produce new California evidence "to assist with the review of ambient air quality standards."

The results of these two studies were published in 2011 and they both found no relationship between PM and total mortality in California. The Jerrett Study found that total mortality during 1982-2000

among about 75,000 California adults was not related to either PM10 or PM2.5 in eight of nine models tested. The Lipsett Study found that total mortality during 2000-2005 among about 75,000 female

California teachers was not related to either PM10 or PM2.5.
The studies found some unexplained evidence of increased cardiovascular disease risk and decreased cancer risk, but there was no overall increased risk of death. These null results agree with the overwhelmingly null results for California that have been published since 2000, which include my 2005 results.

Thus, based on all the evidence described above, there is no health risk associated with PM in the Coachella Valley or in California as a whole and there will be no health risk from PM after the Sentinal power plant is operational. However, since AQMD and others have a different perspective and since The Desert Sun stated that "Robust debate on this issue is needed," I propose that an open forum be organized so that AQMD Executive Officer Barry Wallerstein and I can debate our different views on the health effects of PM in the Coachella Valley. Hopefully, our debate will help resolve the PM health effects issue.

James E. Enstrom is on the research faculty at the UCLA School of Public Health and has been conducting epidemiologic research there since 1973. Email him at jenstrom@ucla.edu

LEARN MORE ABOUT PARTICULATE MATTER
Read the California Energy Commission air quality assessment for the Sentinel plant at mydesert.com/opinion

Websites cited by James E. Engstrom:
www.epa.gov/pm/
www.aqmd.gov/aqmp/07aqmp/aqmp/Chapter_2.pdf
www.epa.gov/ttn/naaqs/standards/pm/s_pm_history.html
cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=216546
www.arb.ca.gov/board/books/2007/012507/07-1-4pres.pdf
wmbriggs.com/blog/?p=4587
ajrccm.atsjournals.org/content/184/7/828.short
www.scientificintegrityinstitute.org/Enstrom081111.pdf

From: "Folmer, James" <jfolmer@palmspri.gannett.com>
To: "James E. Enstrom" <jenstrom@ucla.edu>
Date: Wed, 28 Mar 2012 13:11:05 -0700
Subject: RE: April 5 DSun Op-Ed on PM Health Effects & Enstrom Photo

Photo is fine. I'll try to remember to send you the edited version. Feel free to pester me on Tuesday, but we can never promise exactly when a column will run depending on what's happening in the news.

Thanks.

2000 Krewski Jerrett HEI Report Figure 21
1982-1989 CPS II $PM_{2.5}$ Mortality Risk <1.0 in CA

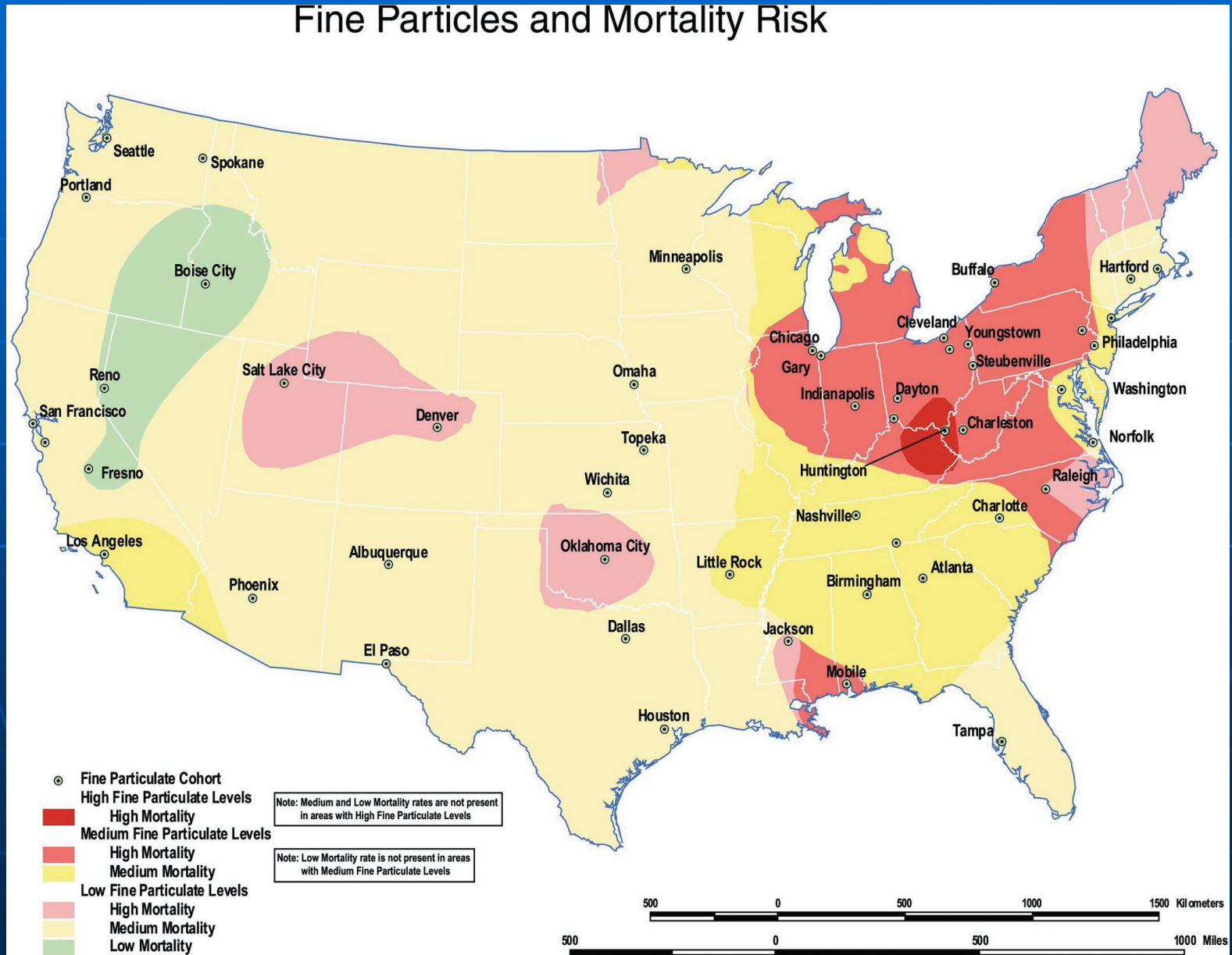


Table 1. Major Epidemiologic Studies of PM2.5 and Total Mortality in California
(http://scientificintegrityinstitute.org/Enstrom081512.pdf)
Relative risk of death from all causes (RR and 95% CI) for increase of 10 µg/m³ in PM2.5

McDonnell 2000 (N~3,800 [1,347 M + 2,422 F]; SC&SD&SF AB Adventists in 9 airsheds, used to estimate PM2.5)	CA AHSMOG Cohort	RR ~ 1.03 (0.95 – 1.12)	1977-1992
Krewski 2000 (2010) (N=40,408 [18,000 M + 22,408 F]; 4 MSAs; 1979-1983 PM2.5; 44 covariates)	CA CPS II Cohort	RR = 0.872 (0.805-0.944)	1982-1989
Jerrett 2005 (N=22,905; 267 zip code areas in LA basin only; 1999-2000 PM2.5; 44 cov + max confounders)	LA Basin CPS II Cohort	RR = 1.11 (0.99 - 1.25)	1982-2000
Enstrom 2005 (N=35,783 [15,573 M + 20,210 F]; 11 counties; 1979-1983 PM2.5; 25 county internal comparison)	CA CPS I Cohort	RR = 1.039 (1.010-1.069) RR = 0.997 (0.978-1.016)	1973-1982 1983-2002
Zeger 2008 (3.1 M [1.5 M M + 1.6 M F]; Medicare enrollees in CA+OR+WA [CA = 73%]; 2000-2005 PM2.5)	MCAPS Cohort "West"	RR = 0.989 (0.970-1.008)	2000-2005
Jerrett 2010 (N=77,767 [34,367 M + 43,400 F]; 54 counties; 2000 PM2.5; KRG ZIP; 20 ind cov+7 eco var; Slide 12)	CA CPS II Cohort	RR ~ 0.994 (0.965-1.025)	1982-2000
Krewski 2010	CA CPS II Cohort		
(N=40,408; 4 MSAs; 1979-1983 PM2.5; 44 cov)		RR = 0.960 (0.920-1.002)	1982-2000
(N=50,930; 7 MSAs; 1999-2000 PM2.5; 44 cov)		RR = 0.968 (0.916-1.022)	1982-2000
Jerrett 2011 (N=73,609 [32,509 M + 41,100 F]; 54 counties; 2000 PM2.5; KRG ZIP Model; 20 ind cov+7 eco var; Table 28)	CA CPS II Cohort	RR = 0.994 (0.965-1.024)	1982-2000
Jerrett 2011 (N=73,609 [32,509 M + 41,100 F]; 54 counties; 2000 PM2.5; Nine Model Ave; 20 ic+7 ev; Fig 22 & Tab 27-32)	CA CPS II Cohort	RR = 1.002 (0.992-1.012)	1982-2000
Lipsett 2011 (N=73,489 [73,489 F]; 2000-2005 PM2.5)	CA Teachers Cohort	RR = 1.01 (0.95 – 1.09)	2000-2005
Ostro 2011 (N=43,220 [43,220 F]; 2002-2007 PM2.5)	CA Teachers Cohort	RR = 1.06 (0.96 – 1.16)	2002-2007

Table 2. Major Epidemiologic Studies of PM10 and Total Mortality in California

Relative risk of death from all causes (RR and 95% CI) for increase of 10 µg/m³ in PM10

McDonnell 2000 (N~3,800 [1,347 M + 2,422 F]; SC&SD&SF AB Adventists with PM10 from CARB monitors) [deaths from all natural causes ICD9=001-799]	CA AHSMOG Cohort	RR ~ 1.01	(0.96 – 1.07)	1977-1992
Chen 2010 (N=4,830 [1,750 M + 3,080 F]; SC&SD&SF AB Adventists with PM10 from CARB monitors) [deaths from all natural causes ICD9= 001-799]	CA AHSMOG Cohort	RR = 1.01	(0.98 – 1.04)	1977-2006
Jerrett 2011 (N=76,135 [33,625 M + 42,510 F]; 54 counties; 1988-2002 PM10; 20 ind cov+7 eco var; Table 37)	CA CPS II Cohort	RR = 1.001	(0.987-1.017)	1982-2000
Lipsett 2011 (N=61,181 [61,181 F]; 1996-2005 PM10)	CA Teachers Cohort	RR = 1.00	(0.97 – 1.04)	2000-2005

FOLLOWING THE SCIENCE: How National Ambient Air Quality Standards (NAAQS) for Particulate Matter (PM) Have Changed Over Time (http://www.epa.gov/pm/agriculture.html)

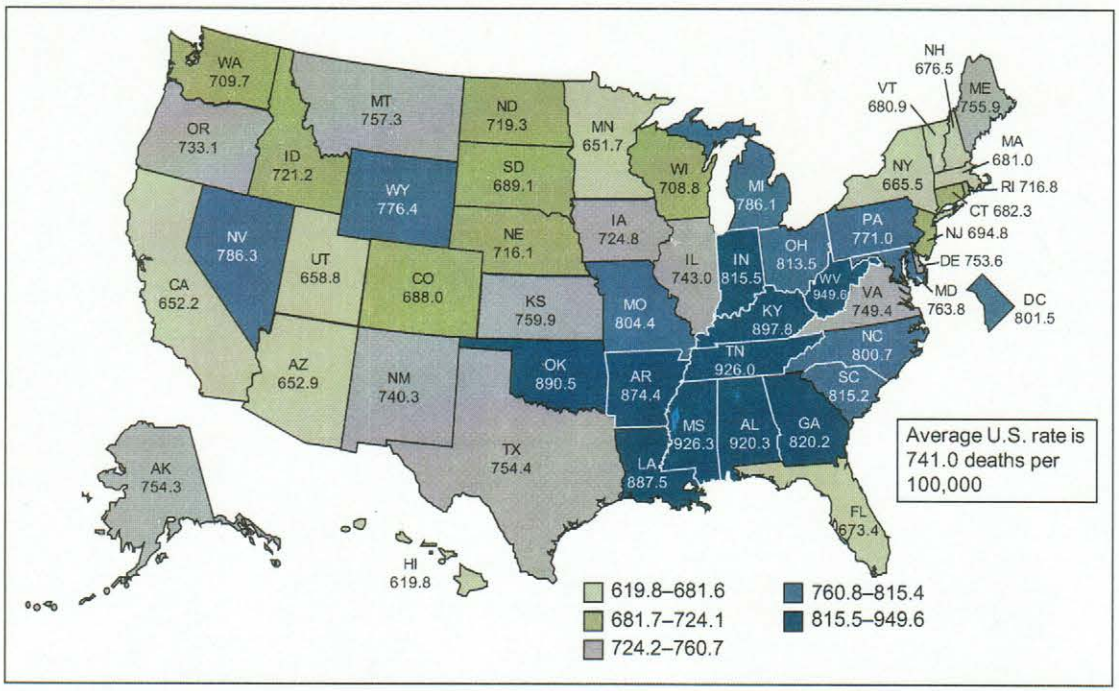
- EPA has regulated particle pollution since 1971. Our standards have evolved over time, as science has taught us more about how exposure to particles affects health and welfare.
- The 1971 standards, for example, set levels for all particles in the air, known as "total suspended particulate." This covered all sizes of airborne particles, including dirt and other larger particles.
- In 1987, EPA changed the standards to focus on those particles 10 micrometers in diameter and smaller, because particles larger than that don't generally get past the nose into the respiratory system. The Agency set both daily and annual PM10 standards at that time.
- In 1997, based on an expanding body of scientific evidence linking fine particles (PM2.5) to serious health effects, EPA added both daily and annual standards for fine particles.
- The Agency revised those standards in 2006, tightening the daily standard. That same year, **EPA revoked the annual standard for PM10, because there was insufficient evidence linking long-term exposure to inhalable coarse particle pollution to health problems.** EPA retained the daily PM10 standard – at 150 micrograms per cubic meter, the same level since 1987.

Do death rates vary by state?

States experience different risks of mortality. Hawaii has the lowest age-adjusted death rate (619.8 deaths per 100,000 population) of all the states, 16.4 percent lower than the average rate for the United States (741.0). West Virginia had the highest state age-adjusted death rate in 2009, 28.2 percent higher than the average U.S. rate.

In general, states in the Southeast region have higher rates than those in other regions of the country. Louisiana, for example, is typical of the region and has an age-adjusted death rate of 887.5 deaths per 100,000 population (3). States in other regions of the country, such as Illinois in the Midwest (743.0 deaths per 100,000 population) and Oregon in the West (733.1 deaths per 100,000 population), have rates that are more comparable with the average U.S. rate (3) (Figure 4).

Figure 4. Age-adjusted death rates, by state and the District of Columbia: United States, preliminary 2009



SOURCE: CDC/NCHS, National Vital Statistics System, Mortality.

Ratio of 2009 Age-Adjusted Total Death Rates (deaths/100,000)

California / U.S.	652.2 / 741.1 = 0.88 = 88%
'South Coast Air Basin' (4 Counties) / U.S.	650.8 / 741.1 = 0.88 = 88%
Los Angeles County / U.S.	637.3 / 741.1 = 0.86 = 86%
Orange County / U.S.	570.9 / 741.1 = 0.77 = 77%

Misrepresentation and Exaggeration of Health Impacts in South Coast Air Quality Management District Revised Draft 2012 Air Quality Management Plan Appendix I Health Effects

and

Request for California Health and Safety Code Section 40471 (b) Hearing on Health Impacts of Particulate Matter Air Pollution in South Coast Air Basin

James E. Enstrom, Ph.D., M.P.H.
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jenstrom@ucla.edu
(310) 825-2048

September 20, 2012

1) In spite of my repeated submissions to AQMD since 2008 of overwhelming evidence of no mortality impacts, including the evidence in my August 30, 2012 Criticism of the Draft 2012 AQMP (http://scientificintegrityinstitute.org/AQMP083012.pdf), the September 7, 2012 Revised Draft AQMP Appendix I Health Effects continues to seriously misrepresent and exaggerate the mortality impacts of criteria pollutants, like particulate matter, in the South Coast Air Basin (http://www.aqmd.gov/aqmp/2012aqmp/RevisedDraft/AppI.pdf).

2) Since 2000, overwhelming epidemiologic evidence that fine particulate matter is not killing Californians has been published by 26 accomplished doctoral level scientists (Ph.D. or M.D.), including myself. Since 2008, extensive written and/or verbal comments by 16 doctoral level critics, including myself, have been submitted to US EPA, CARB, and/or AQMD and these comments strongly criticize the way the California-specific evidence has been characterized by the three regulatory agencies. The names of the scientists and critics are listed on the next page.

3) The 2012 AQMP (http://www.aqmd.gov/aqmp/2012aqmp/index.htm) does not comply with California Health and Safety Code (CHSC) Section 40471 (b): "On or before December 31, 2001, and every three years thereafter, as part of the preparation of the air quality management plan revisions, the south coast district board, in conjunction with a public health organization or agency, shall prepare a report on the health impacts of particulate matter air pollution in the South Coast Air Basin. The south coast district board shall submit its report to the advisory council appointed pursuant to Section 40428 for review and comment. The advisory council shall undertake peer review concerning the report prior to its finalization and public release. The south coast district board shall hold public hearings concerning the report and the peer review, and shall append to the report any additional material or information that results from the peer review and public hearings." (http://www.leginfo.ca.gov/cgi-bin/displaycode?section=hsc&group=40001-41000&file=40460-40471).

4) Before the 2012 AQMP is finalized and approved, the AQMD Governing Board must hold a public hearing on "the report and the peer review" regarding "the health impacts of particulate matter air pollution in the South Coast Air Basin," as required by CHSC Section 40471 (b).

Twenty-Six Doctoral Level Scientists Who Have Published Epidemiologic Findings Since 2000 That Show NO Relationship Between PM2.5 and Total Mortality in California

David E. Abbey, Ph.D., Loma Linda University (2000)
Michal Abrahamowicz, Ph.D., McGill University (2000)
Leslie Bernstein, Ph.D., City of Hope National Medical Center (2011)
Richard T. Burnett, Ph.D., Health Canada, Canada (2000, 2011)
Ellen T. Chang, Sc.D., Cancer Prevention Institute of California (2011)
George Christakos, Ph.D., San Diego State University (2011)
Francesca Dominici, Ph.D., Harvard University (2008)
James E. Enstrom, Ph.D., University of California, Los Angeles (2005, 2006, 2010)
Mark S. Goldberg, Ph.D., University of Quebec (2000)
Katherine D. Henderson, Ph.D., Cancer Prevention Institute of California (2011)
Edward Hughes, Ph.D., Edward Hughes Consulting, Canada (2011)
Michael Jerrett, Ph.D., University of California Berkeley (2010, 2011)
Daniel Krewski, Ph.D., University of Ottawa, Canada (2000, 2010, 2011)
Michael J. Lipsett, M.D., California Department of Public Health (2011)
Aidan McDermott, Ph.D., Johns Hopkins University (2008)
William F. McDonnell, Ph.D., US Environmental Protection Agency (2000)
Bart D. Ostro, Ph.D., California Office of Environmental Health Hazard Assessment (2011)
C. Arden Pope III, Ph.D., Brigham Young University (2011)
Peggy J. Reynolds, Ph.D., Cancer Prevention Institute of California (2011)
Jonathan M. Samet, M.D., University of Southern California (2008)
Yuanli Shi, M.D., University of Ottawa, Canada (2011)
Jack Siemiatyck, Ph.D., University of Quebec (2000)
Michael J. Thun, M.D., American Cancer Society (2011)
George D. Thurston, Ph.D., New York University (2011)
Warren H. White, Ph.D., Washington University (2000)
Scott L. Zeger, Ph.D., Johns Hopkins University (2008)

Sixteen Doctoral Level Critics Who Have Criticized Since 2008 the Relationship Between PM2.5 and Total Mortality in California as Characterized by US EPA, CARB, and AQMD

William M. Briggs, Ph.D., Statistician, New York City & Cornell University
John D. Dunn, M.D., J.D., Physician & Attorney, Darnall Army Medical Center, Texas
James E. Enstrom, Ph.D., Epidemiologist, University of California, Los Angeles
Anthony Fucaloro, Ph.D., Chemist, Claremont McKenna College, California
Gordon J. Fulks, Ph.D., Astrophysicist, Oregon
Michael E. Ginevan, Ph.D., Statistician, M.E. Ginevan & Associates, Maryland
Thomas W. Hesterberg, Ph.D., Toxicologist, Navistar, Illinois
Frederick W. Lipfert, Ph.D., Environmental Scientist, New York
Geoffrey C. Kabat, Ph.D., Epidemiologist, Einstein College of Medicine, New York
Matthew A. Malkan, Ph.D., Astrophysicist, University of California, Los Angeles
Roger O. McClellan, D.V.M., Toxicologist, New Mexico
Henry I. Miller, M.D., Physician, Hoover Institution, Stanford University
Suresh H. Moolgavkar, M.D., Ph.D., Epidemiologist, University of Washington
D. Warner North, Ph.D., Risk Analyst, NorthWorks & Stanford University
Robert F. Phalen, Ph.D., Toxicologist, University of California, Irvine
S. Stanley Young, Ph.D., Statistician, National Institute of Statistical Sciences

Request for a Comprehensive hearing on the Health Impacts of Particulate Matter in the South Coast Basin area in compliance with Section 40471 (b) of the CA Health and Safety Code.

John Dale Dunn MD JD
Emergency Physician Brownwood TX
Policy advisor Heartland Institute, Chicago
Policy advisor, American Council on Science and Health, New York City.
Civilian Contract Faculty, Emergency Medicine, Carl R Darnall Army Medical Center, Fort Hood, TX

Members of the South Coast Air Quality Management District Board of Directors:

The recently released draft for Air Quality Management by the Southern California Air Quality Management District (AQMD) proposes very significant regulatory changes for more than 15 million residents of the area, however the South Coast AQMD proposes these changes without benefit of the prescribed triennial Air quality management plan revisions announcements. In conjunction with an effort to elicit public comments. Draft 2012 is, like so many drafts before, the product of a black box project at the South Coast AQMD, the precautionary principle and acceptance of science that has been effectively challenged in public in the past 4 years.

That is not according to Federal or State Clean Air Act law or the intent of environmental compliance provisions.

The Air Quality Management Plan (AQMP) (http://www.aqmd.gov/aqmp/2012aqmp/index.htm) proposes aggressive and draconian provisions that would have major impacts on the residents of the South Coast Basin Area.

I have included previous submissions to CARB on air regulations that were the product of the 2008-2010 activities and proposals and public comments made by prominent experts opposed to the new CARB air pollution measures. The South Coast Air Management Plan process should include close review and evaluations of those public comments that criticize and conflict with the studies relied on by the District planners.

The economic impact of the Management plan will kill or harm business, industry, transportation, and agricultural activity for now good reason, since air pollution is not killing anyone in South Coast. The proposed AQM Plan will cause hardship and shorten lives for the residents of the area in addition to depressing the economy with the well-known effect that can be expected, higher unemployment, stress and hardship, resulting in shortened life expectancies and misery—all for AQMD chasing a phantom menace—small particle pollution, that by evidence of the studies, causes no harm or deaths.

AQMP also should follow the law, that specifically states at Section 40471 of the Health and Safety Code "On or before December 31, 2001, and every three years thereafter, as part of the

preparation of the air quality management plan revisions, the south coast district board, in conjunction with a public health organization or agency, shall prepare a report on the health impacts of particulate matter air pollution in the South Coast Air Basin. The south coast district board shall submit its report to the advisory council appointed pursuant to Section 40428 for review and comment. The advisory council shall undertake peer review concerning the report prior to its finalization and public release. The south coast district board shall hold public hearings concerning the report and the peer review, and shall append to the report any additional material or information that results from the peer review and public hearings." (http://www.leginfo.ca.gov/cgi- bin/displaycode?section=hsc&group=40001-41000&file=40460-40471).

The district has failed to comply. Therefore they should correct their failure and stand down from pursuing the Plan proposed until the review and hearing process is complete.

For 4 years 2008-2012, the California Air Resources Board (CARB) has attempted to push through air pollution/small particle control regulations that the CARB claimed were based on evidence of human health effects that included deaths from small particles.

Here are the links, which include my previous submissions protesting the inadequacy of the human health effects science relied on by CARB.

Public Comments by experts on the 2008 CARB "Tran" Report

October 24, 2008 CARB Public Comments on Fine PM and Premature Deaths in CA submitted by July 11, 2008
(http://www.arb.ca.gov/research/health/pm-mort/pm-mort_supp.pdf)
(http://www.scientificintegrityinstitute.org/CARBPMComments102408.pdf)

July 11, 2008 CARB PM2.5 Premature Mortality Teleconference Transcript 071108
(http://www.scientificintegrityinstitute.org/CARB071108.pdf)

February 26, 2010 CARB Symposium on PM2.5 & Deaths in CA

February 26, 2010 CARB Symposium on PM2.5 & Deaths Home Page Link
(http://www.arb.ca.gov/research/health/pm-mort/pm-mort-ws_02-26-10.htm)

February 26, 2010 CARB Symposium on PM2.5 & Deaths Agenda & Panel
(http://www.arb.ca.gov/research/health/pm-mort/pm_symposium_agenda.pdf)

February 26, 2010 CARB Symposium on PM2.5 & Deaths Webcast
(http://www.cal-span.org/cgi-bin/archive.php?owner=CARB&date=2010-02-26)

February 26, 2010 CARB Symposium on PM2.5 & Deaths Transcript
(http://www.arb.ca.gov/research/health/pm-mort/symposium_transcript_2-26-10.pdf)

Criticism of June 9, 2011 Draft and October 28, 2011 Final Jerrett Report on PM2.5 Deaths in CA

October 28, 2011Compilation of All Criticism since June 9, 2011 of Jerrett Report on CA PM2.5 Deaths
(http://www.scientificintegrityinstitute.org/JerrettCriticism102811.pdf)

Careful review of the submissions above by previous commenters would justify a stand down from the proposed AQMP outlined by the South Coast MD. Research shows that current ambient air pollution in California is not harmful and doesn't justify aggressive new AQMPlans.

Reputable scientists repeatedly raised important issues and Michael Jarrett's joke of a research project based on his selection of the "conurbation" model data, confirms that the CARB claims of thousands of lives saved by air regs is a house of cards built by CARB on small particle research data dredges to find poorly defined "premature deaths" supposed associated with poorly defined small particle pollution. Such uncertainties certainly cannot justify the extreme elements of the South Coast AMP.

The CARB never was able to properly dispel the objections raised in 2008-2010, and in February of 2010 lost the major face to face debate in a knockout when Dr. Michael Jarrett's project came a cropper and Dr. Jarrett admitted he couldn't find any current air pollution health effects.

Then Dr. Jarrett went back to his computer tricks and decided to redo his research with modeling that is risible, then 9 models showed no effect but one of his ten models finally gave him the results that allowed him to do what CARB asked—support their position that small particles are killers.

Dr. Jarrett's co-authors, an impressive array of fellow travelers in the small particle hunting research community, never excused or explained the decision to rely on the "conurbation" model as more reliable than the 9 models that showed no effect. Although conurbation sounds exotic, it is the game played by researchers called torturing the data, and in this case Dr. Jarrett found a way to dice and chop the geography of California to find populations that had the "associations" of air pollution and deaths he was looking for.

That is called the outcome based research fallacy and is fueled by the fact that Jarrett and his coauthors knew who funded their research, an agency that had a stake in promoting the public perception that small particles are killers.

South Coast Air Management District should comply with California Health and Safety Code Section 40471 (b) and schedule a Hearing for a full vetting of the small particle research issues before implementing the proposed AQMP and then act reasonably and discard the Plan.

There are no impact studies for the past decade, and the AQMD has no reports on health impacts

on record for 2001 through 2010 when there should have been at least 3 reports filed, and at one point an AQMD report said, ignoring its responsibility in reporting, "The purpose of this appendix is to provide an overview of air pollution health effects, rather than to provide estimates of health risk from current ambient levels of pollutants in specific areas of the SCAB." (http://www.aqmd.gov/aqmp/docs/2003AQMP_AppI.pdf).

The health effects studies are the foundation for any management plan and have been discarded in favor of aggressive regulatory proposals based on the precautionary principle or good intentions, but not on the science demanded in the Clean Air Act and its corresponding California Statutes. The research presented to the CARB and the public comments provided make a strong case for no effect from current ambient air pollution. No death effect, no measurable health effect from the criteria air pollutants.

Please consider the comments from 2008 on the proposed CARB Tran report, the submissions made for the debate in February of 2010, and the comments by experts on the final version of the Jerrett study that asserted the "conurbation" model justified the CARB pursuit of new and aggressive small particle regulations.

Many studies have found no PM 2.5 health effect and yet the CARB and the South Coast Management district continue to press forward to the detriment of the California economy. California cohorts have found no relationship between PM2.5 and total mortality. Indeed, detailed analyses of two of these cohorts funded by AQMD and completed in 2011, have found no relationship between any criteria pollutant and total mortality in California (www.scientificintegrityinstitute.org/Enstrom081512.pdf).

The CARB and US EPA human health effects research on small particles and other criteria pollutants have been depended on the questionable methodology of data dredging for "premature deaths. The problem is defining premature deaths, and the studies in fact do not count premature deaths as in a medical investigation, but the noise of variation in death rates. That is an opportunity for irresponsible data torturing to find air pollution and daily variation in death rates to call "premature deaths" that are not. The premature deaths projected by researchers, the USEPA and CARB to thousands in the state or nation are projections of deaths that area more than the daily average, not premature deaths of individuals who have been assessed for confounders and found to die short of life expectancy.

The research is unreliable, and misleading, and projections of hundreds of thousands of lives saved is deceitful nonsense. There are no deaths from small particles, the research is deceptive desk top death certificate data dredging that harvests the noise from day to day death rate variations and calls it signal, then projects the "correlations" the population to make impressive scare numbers of "premature deaths."

These data dredged mortalities are the primary health impact used to justify the NAAQS. So the number is the product of data torturing and deception but even if the AQMD accepts the unreliable counting and methodology, the national standards are not based on health effects or mortality in California or the SCAB. In 2009 the SCAB had an age-adjusted total death rate lower than the death rate in every state in the continental US. (http://www.scientificintegrityinstitute.org/NCHSRR07081l.pdf).

The AQMD is obligated to evaluate the reliability of the research and another consideration is the already mentioned Krewski map that shows no California air pollution effects. That alone should give California policy makers pause before initiating another aggressive regulatory regime.

A good faith effort to review the human health effects science should convince the SC AMD policy makers to reconsider the proposed aggressive Management Plan.

Cordially,

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