Report to EPA
September 2007

Accomplishments of the Particulate Matter (PM) Centers (1999-2005)

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The US 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) that were identified in the National Research Council's (NRC) "Research Priorities for Airborne Particulate Matter" (1998). Research Centers were established at Harvard University, New York University, the University of Rochester, the University of Washington, and a consortium of three universities in Southern California. A midterm report of PM Center findings was published previously (Lippmann et al., 2003). This current report highlights in brief major findings of the PM Centers from the first six years. The PM Centers were structured to bring interdisciplinary research approaches to tackle key knowledge gaps, and this approach promised success in advancing PM science. The collective efforts of the five PM Centers led to significant accomplishments in all the priority research areas identified by the NRC Committee that guided the research program and resulted in a wealth of peer reviewed publications. Substantial supplemental material that provides technical summaries of the data from which the overall accomplishments of the Centers derive can be accessed online at http://es.epa.gov/ncer/science/pm/2008sab/index.html. The supplemental material is organized into chapters on: PM characterization and exposure; health effects including epidemiology and toxicology; and mechanisms of PM toxicity, and contains extensive references to previously published findings.

1. Selected Advances in PM Exposure Research

Characterization of Ambient PM

The PM Centers have significantly advanced the science on characterization of ambient PM and demonstrated that the physical and chemical characteristics of PM vary greatly with region, location, seasonal and diurnal patterns, and size fraction. Selected examples are given here for illustration; for more detail consult the supplemental material to this report. Coarse particles collected in Southern California derive largely from road dust and soil and contain significant quantities of metals, whereas fine particles ($PM_{2.5}$, i.e., PM with aerodynamic diameters <2.5 μm) from the same locations contain primarily nitrates and elemental and organic carbon. Ultrafine PM (UFP) is especially high in organic

carbon (Sardar et al., 2005). In the Pacific Northwest, organic carbon derived from wood burning is a major contributor to fine particle mass (Larson et al., 2006). In the eastern United States, seasonal variations in the composition of $PM_{2.5}$ were reported, with sulfate being more dominant in the summer than in the winter; the fractions of nitrate and organic carbon were relatively higher in winter. An important role for atmospheric chemistry in the size dependent chemical composition of ambient PM has been defined. Atmospheric processes generate UFP in regions of the Los Angeles air basin that receive advected pollutant air masses (e.g. Fine et al., 2004; Kim et al., 2002; Singh et al., 2006). Work in atmospheric chemistry is especially important in relation to a recent report on organic PM showing that photo-oxidation of diesel emissions rapidly generates organic PM (Ntziachristos et al., 2007) and this secondary organic PM derives from semivolatile emissions (Robinson et al., 2007). 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 semi-volatile material that has condensed onto a non-volatile, primarily carbon, core (Kuhn et al., 2005a).

PM Sources

The NRC placed high priority on characterization of PM emissions sources and air quality testing. Accordingly, mobile sources were a major focus of research at the Harvard, Rochester and Southern California PM Centers. PM characterization and toxicological studies were carried out next to roadways and in tunnels. Source apportionment studies frequently identified traffic as a major component of fine and UFP PM mass. A workshop held by the PM Centers to address differences in source apportionment methodology and to conduct comparative research on the outcomes of different analytical methods found good agreement across different investigators and methods in apportioning sources of $PM_{2.5}$ mass in two US cities (Thurston et al., 2005). Effect estimates for a number of sources on cardiovascular mortality were compared across different source apportionment methods; secondary sulfate and traffic were the factors with the greatest effects, and consistency was good (Mar et al., 2006). Specific tracer compounds for PM sources, and atmospheric time of flight mass spectrometry instruments, which analyze compositions of single particles, were used to identify PM sources in ambient samples.

Personal Exposure

The NRC committee also prioritized research on the relationship between personal exposure and ambient measurements from routine monitoring sites, to support interpretation of the epidemiological studies that are the basis of PM risk assessment for regulatory purposes. A significant body of data on personal exposure resulted from the PM Centers' numerous field studies, including longitudinal studies conducted in different airsheds, housing types, and populations. Extensive intra- and inter-personal variability in the ratio of personal to ambient exposure measures and the strength of association were observed (Liu et al., 2003; Wu et al., 2005), but taken collectively the data establish that ambient air $PM_{2.5}$ concentrations at central site monitors can yield valid estimates of average personal exposure for population-based epidemiological 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 indoor PM sources all 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 70-100nm range penetrated indoors to a greater extent than 10-20nm PM (Zhu et al., 2005).

Vapor Phase Co-Pollutant Exposure

The PM Centers studied the relationships between gaseous and particulate ambient air pollutant concentrations in the context of personal exposure studies. In animal studies, concentrated ambient particles (CAPs) and carbon monoxide produced distinctly different cardiac responses in a rat model of myocardial infarction, and no significant interaction was observed between the effects of CO and CAPs in co-exposed animals (Wellenius et al., 2004).

Ambient gaseous pollutant concentrations were better surrogates of personal $PM_{2.5}$ exposures, especially personal exposures to $PM_{2.5}$ of ambient origin, than were personal exposures to the gaseous co-pollutants. These findings suggest both the ambient gaseous and $PM_{2.5}$ concentrations serve as surrogates for $PM_{2.5}$ exposures, and therefore using ambient gas concentrations in multiple-pollutant health effects models with $PM_{2.5}$ may not be appropriate. The robustness of these findings was demonstrated with various analytical methods and model structures (Sarnat et al., 2001, 2002, 2005). In contrast, there was an overall lack of significant associations between hourly and 24-hour UFP number concentration and gaseous co-pollutant concentrations (Sardar et al., 2004), in a Southern California study. In settings characterized by independence of particle number and co-pollutant concentrations, potential confounding effects of co-pollutant exposure on epidemiologic analyses of UFP health effects are mitigated.

Studies conducted in Southern California demonstrated that naphthalene accounted for approximately 80 to greater than 90% of polycyclic aromatic hydrocarbons (PAH) including particle bound PAH (Eiguren-Fernandez et al., 2004). A naphthalene metabolite and product of atmospheric chemistry, naphthoquinone, was demonstrated to generate reactive oxygen species (ROS), and to interact covalently with proteins. Further work on redox active and electrophilic organic compounds in the vapor phase is a priority.

2. Advances in PM Health Effects and Mechanisms of Injury

During EPA's effort to establish a national ambient air quality standard (NAAQS) for $PM_{2.5}$, considerable questions about plausibility of epidemiological findings on hospitalization and mortality from cardiovascular disease arose. As a result the NRC committee prioritized research into the mechanisms of injury that underlie $PM_{2.5}$ health

effects, especially daily mortality. From a policy perspective, the developments in understanding mechanisms and intermediate clinical conditions that could explain the observed cardiovascular mortality are among the highest impact area of the PM Centers' scientific advances. The PM Centers made major advances in the characterization of PM-associated health effects. This summary section highlights some of the relevant areas of success, emphasizing those that were significantly enhanced by a Center-based research approach.

PM Effects on the Cardiovascular System

The research effort on cardiovascular effects of PM extended to epidemiology, human clinical studies, laboratory studies of model animal species, and mechanistic toxicology. New statistical methodology was developed and applied to strengthen the daily mortality studies (Zanobetti et al., 2000; Coull et al., 2001). Epidemiological studies that focused on specific endpoints, such as myocardial infarction (Peters et al., 2001, 2004; Zanobetti and Schwartz, 2005) or cause-specific mortality (Zeka et al., 2005; Franklin et al., 2007) produced hypotheses that were tested in laboratory animal research and human clinical studies. In response to epidemiological advances, toxicologists have worked to identify the cellular and biomolecular mechanisms involved in the cardiovascular effects of $PM_{2.5}$ that result from acute and long-term exposures to concentrated ambient particles (CAPs) (Lippmann et al., 2005b, 2006; Sun et al., 2005; Araujo et al., 2008; Corey et al., 2006). As a result of this significant interdisciplinary effort, plausible mechanisms for $PM_{2.5}$-associated cardiovascular mortality have been proposed and clinical signs and preclinical conditions associated with $PM_{2.5}$ exposure have been identified. Some highlights follow; detailed summaries and additional references may be found in the supplemental material.

Changes in heart rate (HR) and heart rate variability (HRV) due to on-road exposures to highway particles were reported in hypertensive rats (Elder et al., 2007). In a subchronic study of atherosclerosis-prone mice, both acute changes and progressive baseline shifts in HR and HRV were associated with concentrated $PM_{2.5}$ mass (Hwang et al., 2005; Chen and Hwang, 2005). Similar changes were associated with $PM_{2.5}$ nickel content (Lippmann et al., 2006). In humans, panel studies and controlled exposures studies provide mixed evidence of altered HR and HRV. No associations were seen in Seattle during the winter woodburning season (Sullivan et al., 2005; Mar et al., 2005a), while a positive association was observed in the summer in Boston with exposures while on diesel buses (Adar et al., 2007; Schwartz et al., 2005) and in Germany, where changes in the repolarization of the heart in association with $PM_{2.5}$ and the number concentrations of accumulation mode particles were detected (Henneberger et al., 2005). The findings imply that exposure to some sources of $PM_{2.5}$ can affect autonomic control of cardiac function, which may lead to adverse cardiovascular outcomes. Cardiac arrhythmias and vascular changes, such as endothelial cell responses and alterations in blood pressure, are other important clinical signs that were identified in both humans and animals (e.g. Frampton et al., 2006b; Gong et al., 2004; Nadziejko et al., 2002). Atherosclerosis is emerging as an important toxic endpoint of $PM_{2.5}$ exposure. Atherosclerotic lesions in a susceptible mouse model were enhanced by $PM_{2.5}$ exposure in three reports (Araujo et al., 2008; Sun et al., 2005; Chen and Nadziejko, 2005), and a cross-sectional study in humans showed increased carotid intima-medial thickness, a preclinical marker for

atherosclerosis (Kunzli et al., 2005). The atherosclerosis findings may be mechanistically related to reports of myocardial infarction associated with $PM_{2.5}$ in epidemiologic studies (Peters et al., 2004; Zanobetti and Schwartz, 2005).

Investigations in the PM Centers and elsewhere suggest that inflammatory responses are involved in cardiovascular effects. Pulmonary inflammation could lead to the release of reactive oxygen species (ROS), cytokines and chemokines from the lung to the systemic circulation (Frampton et al., 2006b). Alternatively, UFP may gain access to the systemic circulation and act directly on cardiac and vascular tissues. Vascular inflammatory markers were associated with $PM_{2.5}$ exposure in a subchronic inhalation study (Sun et al., 2005). Evidence for an increase in C-reactive protein (CRP) concentrations and a shift to a more pro-coagulating state of the blood was seen in coronary artery disease patients exposed to various size fractions of PM (Ruckerl et al., 2006). Temporal and other parameters differed with the specific air pollution mixture in this study, limiting interpretability.

Respiratory Effects of PM Exposure

Work in the PM Centers has added to a wide body of literature investigating toxicological mechanisms and effects of PM in the respiratory system. Results from clinical and panel studies in asthmatic and elderly subjects, 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 patients and during exercise has important implications for defining populations at greater risk of PM-related effects (Chalupa et al., 2004; Daigle et al., 2003). Numerous studies of inflammatory and pro-inflammatory responses in the airways produced mixed results, but provided little evidence for chronic inflammatory potential of PM. Overall, mechanistic work has developed a body of evidence that indicates PM exposure has the potential to activate inflammatory pathways in target cells of the respiratory system. It is likely that specific PM components are more highly associated with airway inflammatory responses than PM mass. Adjuvant effects of CAPs in promoting allergic airways responses were described 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 (Koenig et al., 2005; Mar et al., 2005b; Jansen et al., 2005). Increased risk of infant hospitalization for bronchiolitis was significantly associated with subchronic and chronic exposures to PM in Los Angeles (Karr et al., 2007). A linkage between the PM Centers and the Southern California Children's Health Study (CHS) produced findings on reduction of lung growth in children exposed to higher levels of PM relative to those less exposed (Gauderman et al., 2004). Indicators of PM exposure were associated with exacerbated asthma, and the effect was enhanced in children in homes with dogs, a marker of endotoxin exposure (McConnell et al., 1999, 2003, 2006a). CHS studies identified traffic as a likely causal factor (McConnell et al., 2006b; Gauderman et al., 2005).

Identification of New Target Tissues

Through dosimetry studies conducted at the PM Centers and elsewhere, it is now known that PM and especially $PM_{2.5}$ and UFP can distribute systemically through the circulatory system. A variety of body tissues are exposed to particles and their soluble components, raising the question of additional target sites for PM toxicity. 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 toxicological target. In support, findings from studies of mice chronically exposed to CAPs documented loss of brain neurons (Veronesi et al., 2005) and changes in gene expression consistent with inflammatory effects in brain tissues (Gunnison and Chen, 2005). The levels of two proinflammatory cytokines were increased in brain tissue of mice exposed to particulate matter compared to that of control animals (Campbell et al., 2005).

A study of traffic density, PM exposure, and low birth weight suggested that the developing fetus may be affected by maternal PM exposure (Wilhelm and Ritz, 2003), in agreement with a growing body of literature. Toxicological studies are needed to follow up the epidemiological findings of effects on the fetus.

Chemical Mechanisms of PM Toxicity

Experimental linkages between PM characterization studies and toxicological or clinical effects are critical to identify the most toxic PM components and sources that pose the greatest risks to public health. The PM Centers have produced many studies that describe toxicological properties associated with specific physical/chemical characteristics of PM, including size, surface area, and components, such as transition metals, endotoxin, and organics, including reactive organic compounds. Work in the PM Centers has identified multiple chemical and biological mechanisms by which PM can induce toxic effects in a variety of target cell types; for detailed mechanistic results, the reader is referred to the supplemental material accompanying this report. Brief highlights follow.

Studies of reactive chemical components of ambient PM samples reported that particles possess intrinsic chemical reactivity that may play an important role in toxicity (Venkatachari et al., 2005; Cho et al., 2005; Pan et al., 2004). Covalent modification of biological molecules by reactive chemical compounds, particularly organics, and production of ROS are two key chemical mechanisms by which PM or its components 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 that particles can directly inhibit the activity of enzymes involved in oxidative stress response in a cell free assay (Hatzis et al., 2006). The PM Centers developed a large body of findings to support a growing literature on mechanisms related to oxidative stress and pro-inflammatory responses in cultured cells and laboratory animals. A strong evidentiary basis for oxidative damage, as a general toxicological mechanism of PM injury, has been established (Tao et al., 2003; Gonzalez-Flecha, 2004; Rhoden et al., 2004, 2005 ; Delfino et al., 2005; Xia 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. Elevated oxidative chemiluminescence in heart and lungs of rats was observed after exposure to CAPs and residual oil fly ash (Gurgeira, 2002). An important role of metals may be alteration of signal transduction pathways involving oxidative stress, signaling through the epidermal growth factor receptor (Samet et al., 2003). Oxidative stress has been linked with cellular and molecular changes and inflammatory processes, and is potentially relevant to a wide range of intermediate markers and health effects associated with PM exposure. Assays that can screen for both oxidative and covalent binding properties of PM are excellent candidates for application to comparing the toxicological potential of PM from different sources, locations of interest, seasons, and other parameters of interest (Borm et al., 2007). While considerable progress has been made in elucidating mechanisms of PM toxicity, new toxicological endpoints associated with PM exposure have been identified through research at the Centers and elsewhere, thereby requiring additional efforts to link health endpoints with mechanisms and with specific characteristics of PM.

Life Shortening Associated with Exposure to Particulate Matter

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 most of the effect of air pollution is not simply to advance death 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 were considered and becomes five times higher for respiratory mortality (Zanobetti et al., 2003). Furthermore, reduction of air pollution resulted in 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) and Laden et al. (2006).

Susceptibility Factors and Populations of Concern for PM-Induced Health Effects

When the PM Centers research was initiated, epidemiological 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 produced research findings that expand the spectrum of populations of concern.

Support for the epidemiological observations that elderly and chronic obstructive pulmonary disease (COPD) 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 (see supplemental material). Further support for the elderly as a population of concern comes from studies of geriatric laboratory animals (Elder et al., 2004a). Dosimetry studies reported that increased airway deposition of PM may explain increased risk observed in people with lung disease.

Epidemiological and clinical studies that include potentially susceptible subgroups, or assess effect modification by individual characteristics and conditions that may confer susceptibility, have worked together with toxicological studies of compromised animal models to identify new factors that may increase individual susceptibility to the adverse effects of PM exposure. In epidemiological studies, the PM Centers contributed to work that identifies infants and children as an important population of concern for respiratory effects of PM, evidenced by decreases in lung development and increases in asthma and asthma symptoms (Gauderman et al., 2005, 2007; McConnell et al., 2006a; Molitor et al., 2007; Trenga et al, 2006). Associations between fine PM and increased hospitalization rates of infants for bronchiolitis were reported, identifying infants as susceptible to fine PM exposure (Karr et al., 2007). 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 a 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). One hypothesis for the susceptibility of diabetics that was explored by PM Center research is 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 Centers (Frampton et al., 2006a). People with cystic fibrosis likely constitute a sensitive population; cystic fibrosis patients had increased risk of exacerbations and a decline in lung function associated with a PM exposure metric (Goss et al., 2004). Respiratory infection, especially pneumonia, confers a greater risk of adverse health effects in both epidemiological and laboratory animal studies. Six months of daily CAPs inhalation exposures in an atherosclerotic mouse model produced evidence of greater PM-associated effects on heart rate variability in comparison to the parental strain (Chen and Hwang, 2005), supporting epidemiological results that people with existing cardiovascular disease have higher risk of mortality.

3. Advances in Critical Interdisciplinary Research Areas

Interdisciplinary research has been a hallmark of the PM Centers since their inception. Three subject areas in which the PM Centers have made impacts stand out as exemplary of the success of bringing together multiple investigative perspectives: studies of UFP, mobile sources, and long range transport.

Ultrafine Particles: Unique in Composition and Toxicity

The Center context was exceptionally important for investigations of UFP. A major effort to characterize size distributions, chemical speciation and the effect of atmospheric processes of UFP was integrated into a strong body of toxicological research that has expanded current understanding of UFP toxicities. UFP in urban airsheds are largely derived from fresh combustion sources, although secondary formation of UFP from

atmospheric photochemical processes is also important (Sioutas et al., 2005). UFP dominate particle number concentration in ambient PM samples, and a significant fraction of daily personal exposure to UFP may be received during in-vehicle exposure (Zhu et al., 2007). Due in part to a complex fractal structure (Friedlander and Xiong, 2000), UFP possess much greater surface area per unit mass than other ambient particles, and larger concentrations of adsorbed or condensed toxic air pollutants (oxidant gases, organic compounds, transition metals) per unit mass (Sioutas et al., 2005); these properties have the potential to confer a higher per mass toxic potency on UFP relative to larger and more simply structured particles. Indeed, studies on ambient and model particles have concluded that the large specific surface area of UFP is a key component in their toxicology (Oberdorster, 2001; Donaldson and Stone, 2003).

The PM Centers produced an integrated body of exposure and toxicological studies on ambient and model UFP as well as studies of controlled human exposures. Dosimetry work was a key contribution. Kreyling et al. (2006) reviewed UFP-lung interactions and argued that given the continuous nature of the inhalation of insoluble UFP, these particles will have significant accumulation in the lung and secondary organs. The potential for translocation from the site of lung deposition into systemic circulation has major mechanistic implications (Elder and Oberdorster, 2006). Center investigators found that UFP can lodge in mitochondria; disruption of mitochondrial functions may play an important role in PM-mediated health effects (Xia et al., 2007). PM Centers have contributed to a key advance in the toxicology of UFP in recent years: establishing the ability of UFP to induce oxidative stress and inflammation in experimental systems. The use of concentrators that provided PM samples at different size fractions has allowed mechanistic experiments that substantiate the biological plausibility of epidemiological effects associated with $PM_{2.5}$ mass concentration, and importantly provided ambient UFP for toxicological research.

In a study of 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. (2003) summarized contrasting features of coarse, fine and ultrafine particles from Southern California, including relevant chemical and biological parameters. In that set of studies, UFP were more potent than fine and coarse PM in inducing oxidative stress, as measured by three *in vitro* assays. Electron microscopy also indicated subcellular penetration and mitochondrial damage by UFPs and, to a lesser extent, fine particles. The toxicological findings correlated with $PM_{2.5}$ organic carbon and PAH composition, suggesting a role of organic agents in generating redox activity. In an animal toxicology study UFP-only exposure had greater atherogenic potential in comparison to the fine plus UFP fraction (Araujo et al., 2008).

Expanded focus in epidemiologic research on the UFP fraction is needed, but this has been hampered by a relative lack of exposure data and the complex issues involved in assessing exposure to UFP. Exposure challenges include high spatial variability in source and concentration of UFP, indoor sources, variable infiltration of UFPs from a variety of outside sources, and meteorological factors leading to high seasonal variability in concentration and composition, including volatility.

Traffic: Mobile Sources are Highly Relevant to the Public Health Impacts of PM

In the first six years, the PM Centers collectively produced an important body of research that addressed the public health impacts of mobile source PM. A highly interdisciplinary and well-integrated approach produced findings ranging from characterization of emitted particles and particle chemistry to toxicological and human health studies. The Center-based research context was particularly useful in advancing the science in the area of mobile source research, which is the focus of an extensive international research effort. Within the context of PM Centers, the physical and chemical characteristics of mobile source PM could be more effectively linked to toxicological and health studies, increasing the options for data analysis and greatly enriching the implications of resulting study outcomes.

Numerous investigations of the physical and chemical attributes of PM collected alongside busy freeways and in freeway tunnels, with a focus on UFP, were performed. The results have yielded a wealth of data on size distribution, number and mass concentrations, chemical speciation, emissions factors, volatility, penetration indoors and the impact of atmospheric processes on roadway PM (Fine et al., 2004; Kuhn et al., 2005b, 2005c; Zhu et al., 2005; Sardar et al., 2005; Geller et al., 2006; Biswas et al., 2007; Phuleria et al., 2007; Kittelson et al., 2004). Detailed spatial profiles of roadway PM were measured at varying distances from California freeways (Zhu et al., 2002a, 2002b). These studies showed that concentrations of UFP dropped exponentially with distance reaching upwind levels at approximately 300 meters from the middle of the freeway, and the size distribution of UFP also changed markedly with distance, reflective of coagulation and other atmospheric particle processes. Exposure to motor-vehicle exhaust emissions during commuting may constitute a substantial fraction of daily personal PM exposure, especially to UFP (Zhu et al., 2007). Research in this area provides critical information to enhance interpretation of epidemiological studies that investigate how exposure to roadway traffic may modulate health outcomes.

Toxicological 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 and stimulation of pro-inflammatory effects such as altered gene expression in cellular test systems. UFP fraction, carbonaceous content, and an organic tracer for vehicles were linked with activity in a variety of assays (Li et al., 2003; Cho et al., 2005). Several studies of laboratory animals exposed to CAPs on or near busy roadways have identified cardiovascular and allergic airways effects (Elder et al., 2004b, 2007; Kleinman, 2005). A small study of brain tissue from freeway-exposed mice reported changes consistent with an inflammatory response in central nervous system tissue (Campbell et al., 2005). Evidence that traffic-derived air pollution affects humans has expanded significantly during the first six years of PM Centers funding, to implicate mobile sources in respiratory effects in children (McConnell et al., 2006b; Gauderman et al., 2005), 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). 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). A novel exposure error

approach (Schwartz and Coull, 2003) found that carbon monoxide had an effect in the National Morbidity and Mortality Air Pollution Study; the authors suggested that traffic exposure might be responsible for the mortality effect (Zeka and Schwartz, 2004). These findings demonstrate the importance of a focused effort on mobile source pollutions as well as stationary sources powered by fossil fuels. We believe the scope of the potential problems is only now being recognized.

Long-Range Transport of Regional PM Affects Large Populations

The excess annual mortality in U.S. urban areas that has been demonstrated by the cohorts studied in Six-Cities (Laden et al., 2006), American Cancer Society (Pope et al., 2002, 2004), and Women's Health Initiative (Miller et al., 2007) represents the greatest public health impact of $PM_{2.5}$ and of air pollution as a whole. Since $PM_{2.5}$ is a relatively stable regional pollutant, it affects very large populations within, between, and downwind of urban areas, especially in the Midwest and east coast. PM Center studies brought a powerful interdisciplinary approach to studies of regionally transported PM that establish health effects relevant to these large populations.

The subchronic inhalation studies of mice predisposed to atherosclerosis performed by the NYU PM Center demonstrate the relevance to public health of long-range regional sources. In two six-month studies, mice prone to atherosclerosis and healthy control mice were exposed to $PM_{2.5}$ concentrated 10-fold (Lippmann et al., 2005a; 2005b; 2006). The study site was free of local PM sources. Despite the relatively low levels of exposure, there were significant health-related effects, including both acute and chronic changes in HR and HRV (Hwang et al., 2005; Chen and Hwang, 2005), aortic plaque development (Chen and Nadziejko, 2005), degeneration of dopaminergic neurons (Veronesi et al., 2005), and altered gene expression patterns in heart and lung tissue (Gunnison and Chen, 2005). In a parallel *in vitro* exposure study involving source apportionment, NF*k*B expression in lung cells was significantly associated with a residual oil combustion source factor which represented 2% of the $PM_{2.5}$ mass and was marked by vanadium and nickel (Maciejczyk and Chen, 2005). In a companion study on mechanisms underlying the cardiovascular effects, *in vitro* analyses of tissues from the mice that are genetically prone to atherosclerosis showed that the subchronic CAPs exposures produced altered vasomotor tone, vascular inflammation, and enhanced atherosclerosis (Sun et al., 2005). These subchronic CAPs inhalation studies in a mouse model of atherosclerosis provide biologic plausibility for the excess cardiovascular mortality seen in the cohort studies and identify long range transport of PM as important to public health impacts.

4. 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 NAAQS for PM, but also on characterizing exposures and their distributions in compliance analyses and in devising control strategies for protecting public health.

The findings of mortality and morbidity that form the scientific basis for the short-term and annual PM NAAQS were strengthened through epidemiological and statistical work. Mechanistic investigations and studies of preclinical markers established strong biological plausibility for observed relationships between ambient air PM and observed daily and annual mortality. Validation of relationships between personal and central site ambient concentrations has been crucial to the interpretation of epidemiological results.

To date, EPA has established PM NAAQS based on mass concentration. Findings from the PM Centers and other investigators on particle numbers, surface area, composition and related toxicity of UFP have raised key questions about the adequacy of the mass based standards for public health protection. The potential efficacy of number and component based standards should be assessed. 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 toxicological endpoints that have been associated with PM and a more sophisticated approach to PM NAAQS will be needed. As more information becomes available to link specific PM emissions sources, chemical composition, and physical characteristics with quantitative measures of toxicity, the question of source-specific controls to maximize public health protection may also need to be considered.

The importance of UFP has raised other key 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 also potential environmental justice concerns associated with transportation derived combustion, since it is often areas of lower socioeconomic status that are most affected by proximity to these sources.

Other key policy issues have emerged from the contributions of the scientific findings of the PM Centers. These include the demonstration of chronic effects of air pollution on lung growth in children and on lung cancer in adults. Development of atherosclerosis and other indicators of cardiovascular disease may be a critical chronic effect of PM exposure; existing NAAQS require review to assess the extent of protection against these chronic effects. Identification of new health endpoints and target tissues associated with PM exposure also pose policy challenges – to assure that NAAQS are adequate to protect against developmental effects in the fetus, for example, or central nervous system effects. The data on susceptible populations has been expanded, and existing NAAQS must be evaluated to assure that the populations at greatest risk are protected.

5. 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 that were identified during the development of the 1997 PM NAAQS are still of critical relevance today, but the scientific questions being asked have been refined.

The current PM Centers at Southern California, Harvard and Rochester, joined by new centers at the University of California at Davis and Johns Hopkins University, continue to apply multidisciplinary approaches to the overall research agenda.

Particle Source Characterization and PM Components as Factors in PM Toxicity

The PM Centers present research agenda includes sophisticated and detailed studies of the physical and chemical attributes of ambient PM associated with specific sources. There is an overarching emphasis on continuing to expand the current knowledge base concerning how the physical-chemical characteristics of PM determine which pathophysiological responses, and ultimately which adverse health outcomes, occur in response to PM exposure. The current science indicates multiple mechanisms of injury, in backgrounds modified by host susceptibility factors, are activated by a variety of PM components and characteristics. One approach to this complexity is to attempt systematic evaluation of qualities such as particle size, surface area, chemical composition, and then define the relationship of these factors to toxicity as measured by a defined set of assays. *In vitro* studies will pay particular attention to UFP and to organic compounds and transition metals. UFP formed from nucleation of ambient air vapors are a new focus, as they may be especially toxic. Another approach being undertaken in the current PM Centers agenda is to compare toxicological properties of PM by source type. Mobile sources continue to be a priority focus; 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 six years of PM Center work, the current PM Centers include human panel studies and toxicological studies in laboratory animals and *in vitro* systems that test hypotheses about the effects of mobile source particulate exposures. Source apportionment efforts are ongoing, as well, to build on previous work that found mobile sources are dominant contributors to urban ultrafine particle loads.

Co-pollutants

The PM Centers research portfolios have emphasized the relative importance of combinations of various pollutants to health responses, so that relevant pollutants can be regulated appropriately. The PM Centers are located in diverse sites, which creates the opportunity to investigate PM and health effects in multiple locations with different pollution characteristics, together with local or common co-pollutants. Ongoing epidemiological and toxicological studies are addressing the influence of co-pollutants on health responses to PM.

Dosimetry and Toxicokinetics

Research at the PM Centers is addressing particle deposition, uptake, distribution, and fate, including the effects of developmental stage on deposition of PM. Cell culture systems are being used for studies of metabolic and genetic responses. Studies of the dosimetry and toxicokinetics associated with UFP are especially important given the previous Centers' findings that these particles distribute into systemic circulation 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 of interest currently include reactive chemical species that cause cellular oxidative stress responses, which in turn may contribute to the development of downstream adverse effects including asthma and atherosclerosis. In the first six years, studies of oxidative damage associated with PM were performed in chemical studies, cell culture experiments and laboratory animal studies. Evolving out of that work, the current PM Centers include studies that are look at markers of oxidative stress processes in humans, and a range of clinical and pre-clinical signs.

Research Methods

The PM Centers program is building on past methodological advances as well as introducing new methods for PM research. Particle concentrators and samplers continue to be central to the overall research strategy of the PM Centers, linking ambient air particle sources to laboratory experiments and exposure measurements for toxicological and epidemiological studies. Chemical speciation of ambient PM is key. In response to methodological challenges that arise from the high variability and physico-chemical complexity of ambient PM, upcoming research will also include greater use of laboratory-manufactured model particles, including particles with adsorbed chemical components of interest. Model particles can also address some limitations in collecting sufficient ambient material for some laboratory applications. Microarray approaches and other methods of studying genetic responses in various cell types is receiving increased attention because results from previous PM Center research in cellular systems *in vitro* and in epidemiological studies have identified potentially relevant genes to study. The list of gene products that can be used as indicators of PM exposure or toxicity in various cell types has expanded. A range of epidemiological study designs are being applied, and there is a trend toward measurement of an enhanced array of intermediate markers of cardiovascular effects. In addition, for study designs that allow it, most include detailed exposure measurements that will provide a range of possible explanatory variables for analysis.

Susceptibility

Susceptibility is a major theme, drawing on the work from the earlier Center and non-Center investigators showing that individuals with pulmonary and cardiac health conditions, the 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, and 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.

6. Conclusions

In 1998, a committee of the National Research Council (NRC) published the first of a 4 volume report series entitled: "Research Priorities for Airborne Particulate Matter" identifying the 10 highest priority targets for PM research (NRC 1998). These included:

- Research Topic 1: Outdoor Measures Versus Actual Human Exposures
- Research Topic 2: Exposures of Susceptible Subpopulations to Toxic Particulate-Matter Components
- Research Topic 3: Characterization of Emission Sources
- Research Topic 4: Air-Quality Model Development and Testing
- Research Topic 5: Assessment of Hazardous Particulate-Matter Components
- Research Topic 6: Dosimetry: Deposition and Fate of Particles in the Respiratory Tract
- Research Topic 7: Combined Effects of Particulate Matter and Gaseous Pollutants
- Research Topic 8: Susceptible Subpopulations
- Research Topic 9: Mechanisms of Injury
- Research Topic 10: Analysis and Measurement

Within the PM Centers' research portfolio, it is apparent that each of these priority areas is being addressed. Furthermore, a subsequent NRC report (2001) emphasized that these research priorities require multidisciplinary approaches but that institutional and cultural obstacles often discourage attempts to do research across disciplines and institutions. The PM Centers have overcome this limitation with the requirement of a multidisciplinary and highly integrated group of investigators and with oversight from an expert external Scientific Advisory Panel charged not only with reviewing the science but also its relevance and programmatic integration. To further address the challenges of integration across the PM Centers, investigators have met formally on an annual basis to review their findings and to identify multicenter research opportunities and informally in a variety of settings to support these collaborative activities. 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 undoubtedly represent the very best opportunity in breaking down the barriers that limit the essential cross-fertilization. It is probably too early to fully judge the success of the PM Centers' Program, but much progress has been made and the next 5 years of this program should be instrumental in addressing key scientific and public health policy issues.

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