PM Health Effects Research: Supplement to *Accomplishments of the Particulate Matter (PM) Centers (1999-2005)*

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This EPA Website document summarizes the progress made by the EPA PM Centers in identifying and understanding the health effects of PM air pollution since the mid-course report prepared in 2002 (Lippmann et al., 2003).

When the PM Centers were designated in 1999, the primary body of evidence for health effects of PM consisted of epidemiologic studies of associations of short-term PM concentrations with daily mortality and long-term average PM with long-term mortality. In the first six years of the PM Centers program there was substantial work to understand and assess potential flaws and weaknesses in this body of evidence, and to develop an understanding of the mechanisms underlying these associations. In the more recent work, the PM Centers research has substantially expanded the range of clinical and preclinical health effects indicators associated with PM exposures. With respect to toxicological studies, both in experimental animals and *in vitro*, increasing efforts were devoted to using real-world particles and exposures (e.g., use of ambient PM concentrators) and mimicking human conditions of compromised organ functions in animals for evaluating PM effects. While interest has continued in measuring the respiratory effects of PM, much of the recent research has focused on identifying and understanding the cardiovascular health effects of $PM_{2.5}$ exposures.

MORTALITY

The Harvard Six Cities and the American Cancer Society Cancer Prevention II (ACS) prospective cohort studies provided some of the most important evidence to support the 1997 and 2006 $PM_{2.5}$ annual average NAAQS. Extended mortality follow-up of the ACS cohort for nine more years more than doubled the number of deaths observed. The extended ACS cohort follow-up verified that cardiopulmonary mortality was significantly associated with $PM_{2.5}$, that excess annual mortality was not associated with larger particles, and that there was a significant association of $PM_{2.5}$ with lung cancer (Pope et al., 2002). The extended follow-up of the Harvard Six-Cities cohort for eight more years approximately doubled the number of deaths observed (Laden et al., 2006). $PM_{2.5}$ concentrations for the extended follow-up years were estimated from PM_{10} and

visibility measures. $PM_{2.5}$-mortality associations were observed for all-cause mortality equivalent to those found in the original analysis. However, $PM_{2.5}$ concentrations were substantially lower in the extended follow-up period than in the original analysis, especially for two of the most polluted cities. Reductions in $PM_{2.5}$ concentrations were associated with reduced mortality risk, and were largest in the cities with the largest declines in $PM_{2.5}$ concentrations. These results suggest that improvements in air quality lead to extended life expectancy. The extended ACS cohort analyses also examined the contributions of each subcategory of excess cardiopulmonary deaths to the total excess, and reported that a very large percentage was due to cardiovascular causes (Pope et al., 2004), stimulating an increase in PM Center focus on cardiovascular effects research. In addition, a recent study, based on 65,893 postmenopausal women in 36 US cities in the Women's Health Initiative (WHI) cohort (Miller et al., 2007) reported that the risk of death from cardiovascular disease was significantly associated with chronic exposure to $PM_{2.5}$.

CARDIOVASCULAR MORTALITY AND MORBIDITY

There is a large body of literature showing associations of cardiovascular mortality with PM. Recent studies have attempted to better understand the pathways of these associations through examination of associations with specific cardiac events, measurements of preclinical markers of cardiac events and risk for such events, and the development and application of technologies for laboratory studies focused on the environmental and host factors that cause or contribute to the expression of adverse cardiovascular events.

Cohort Studies

In the extended follow-up of the Harvard Six Cities cohort, the strongest associations were seen with cardiovascular mortality, specifically a 28% increased risk of cardiovascular mortality associated with each 10 $\mu g/m^3$ increase in average $PM_{2.5}$ (Laden et al., 2006). Moreover, the strongest indication of benefits was also seen with cardiovascular mortality. For each 10 $\mu g/m^3$ reduction in $PM_{2.5}$ in the extended follow-up, there was an estimated 69% lower cardiovascular mortality.

In analysis of cause-of-death data in the ACS study, (Pope et al., 2004) long-term $PM_{2.5}$ exposures were most strongly associated with mortality attributable to cardiovascular causes, specifically ischemic heart disease, dysrhythmias, heart failure, and cardiac arrest. For these cardiovascular causes of death, a 10-$\mu g/m^3$ elevation in $PM_{2.5}$ was associated with 8% to 18% increases in mortality risk. This suggests that $PM_{2.5}$ is a risk factor for cause-specific cardiovascular disease mortality via mechanisms that likely include systemic inflammation, accelerated atherosclerosis, and altered cardiac autonomic function.

In the WHI cohort (Miller et al., 2007), a 10-$\mu g/m^3$ increase in $PM_{2.5}$was associated with a 76% increase in CVD death, as well as a 24% increase in a CVD event (coronary revascularization, myocardial infarction, and stroke, as well as death).

Time-Series Studies

While the investigation of specific causes of death provides insights into possible pathways, there is a cost in reduced statistical power to detect associations because of smaller numbers of events. One approach to reduce this loss of power is to pool event data across multiple cities. In analysis of daily mortality in 20 US cities all-cause and cardiovascular mortality was positively associated with PM_{10} on the previous two days (Zeka et al., 2005). Hospital emergency visits for myocardial infarction among the elderly in 21 US cities increased by 0.65% associated with each 10 $\mu g/m^3$ increase in ambient PM_{10} (Zanobetti and Schwartz, 2005).

Other studies have also assessed associations with myocardial infarctions. Case-crossover analyses of diary data collected in 691 myocardial infarction survivors indicated that time spent in traffic was associated with an almost three-fold increased risk of a myocardial infarction 1 hour later (odds ratio 2.9) (Peters et al., 2004). Time spent in cars, on public transportation, or on motorcycles or bicycles were each linked with an increase in the risk of myocardial infarction, suggesting a specific link to traffic pollution. On the other hand, case-crossover analysis of almost 6,000 confirmed myocardial infarctions in Seattle (Sullivan et al., 2005a) found no increased risk associated with particle concentrations measured by nephelometry in the previous 24 hours.

If PM is associated with ischemic cardiac events, then we should also expect associations with other ischemias. In Boston, increased ambient particle levels were associated with transiently increased risk of ischemic but not hemorrhagic stroke (Wellenius et al., 2005).

Cardiac readmissions among myocardial infarction survivors in five European cities increased in association with concentrations of PM_{10} particle number, and also with CO, NO_2 and O_3 concentrations (von Klot et al., 2005). PM_{10}, CO, NO_2 and SO_2 were associated with the rate of hospital admissions for congestive heart failure in Pittsburgh (Wellenius et al., 2005). Patients with recent myocardial infarction were at the greatest risk of particle related admissions.

In summary, studies of cause-specific daily mortality, hospital admissions, and emergency department visits show associations of PM with more specific indicators of cardiovascular events, including myocardial infarction, readmission following myocardial infarction, congestive heart failure, and ischemic stroke.

INTERMEDIATE MARKERS OF CARDIOVASCULAR EFFECTS

Given the evidence that the frequency of clinical cardiovascular events is associated with PM, studies of physiological, preclinical markers of cardiovascular disease provide evidence of health effects and insights into potential pathways. Repeated measures studies have analyzed the effects of ambient PM on a wide range of pre-clinical markers of health response among healthy or compromised subjects in the community in both clinical experiments and animal models. These studies have considered a range of potential pathways: including cardiac arrhythmias; autonomic function measured by heart rate (HR) and heart rate variability (HRV); vascular changes, including blood pressure and vascular reactivity; and inflammatory markers.

Cardiac Arrhythmias

Population Studies: The observed associations of PM with sudden cardiac death suggest a possible role of cardiac arrhythmias. Cardiac patients in Boston with implanted cardioverter defibrillators followed for an average of three years (Dockery et al., 2005) had higher rates of ventricular arrhythmias associated with air pollution over the previous two calendar days. Significant associations were found only for patients who had a previous arrhythmia within the previous three days. A case-crossover analysis of these data (Rich et al., 2005) found $PM_{2.5}$ concentrations in the prior 24 hours was significantly associated with higher risk of ventricular arrhythmias.

In a panel study of elderly Boston residents (Gold et al., 2005), a decreased ST segment in the ECG (an indicator of possible myocardial ischemia or inflammation) was associated with increased ambient concentrations of particles, specifically of BC.

Laboratory Animal Studies: Animal studies have found similar associations. In rats with a surgically induced myocardial infarction, there were marked increases in post-MI arrhythmias (premature ventricular complexes) following exposure to residual oil fly ash (ROFA) in animals with a history of arrhythmias, compared to those exposed to room air (Wellenius et al., 2002). Aged rats showed a significant increase in the frequency of irregular delayed beats after exposure to CAPs, which was not seen after exposures to ultrafine carbon, to air, or to SO_2 (Nadziejko et al., 2004).

Ambient air pollution is a complex mixture of PM and gaseous co-pollutants, such as CO. Rats with induced myocardial infarction were exposed (1 hour) to either filtered air, CO alone, CAPs alone, or CAPs and CO (Wellenius et al., 2004). CO exposure significantly reduced ventricular premature beat frequency, while CAPs exposure increased VPB frequency during the exposure period, although this effect did not reach statistical significance, and was modified by the number of pre-exposure VPBs. Neither CAPs nor CO had any effect on HR, but CAPs increased HR in specific subgroups.

Autonomic Control of the Heart

Population Studies: Studies in both humans and animals have shown $PM_{2.5}$ to be associated with autonomic control of the heart as measured by HR and HRV, a measure of sympathetic/parasympathetic tone and autonomic function. These complementary findings in human panel and controlled CAPs exposure studies demonstrate that increased levels of $PM_{2.5}$ are able to perturb cardiac autonomic function, which may lead to adverse cardiovascular outcomes.

In a panel of elderly subjects in Boston seen repeatedly over twelve weeks, $PM_{2.5}$ was associated with decreased HRV (Schwartz et al., 2005a). Specific associations were found with BC, an indication of traffic particles, and with secondary particles, an indicator of long-range transport. In a panel of 56 men with ischemic heart disease in Erfurt, Germany, changes in repolarization of the heart were associated with $PM_{2.5}$ and also with OC and EC concentrations in the ambient air (Henneberger et al., 2005). A panel study of eighty-eight older healthy or subjects with lung or heart disease in Seattle (Mar et al., 2005) found associations between decreased HR and $PM_{2.5}$ in healthy subjects. However, a study of elderly subjects with and without cardiovascular conditions in Seattle showed no association between outdoor PM measured by nephelometry and HRV (Sullivan et al., 2005b).

In chamber exposure studies of 12 healthy adult and twelve asthmatic volunteers exposed to filtered air or CAPs (~200 $\mu g/m^3$) for 2 hours, both healthy and asthmatic subjects showed CAPs-related parasympathetic stimulation of HRV (Gong et al., 2003). Acute exposure to elevated concentrations of ambient CTPM also altered the autonomic nervous system of the heart in adult volunteers (Gong et al., 2004).

UFP in ambient air may play a role in cardiovascular effects. In randomized controlled studies (Zareba et al., in press) healthy subjects exposed to filtered air and to EC UFP for two hours with intermittent exercise showed a small, but not clinically significant increase in parasympathetic tone and a shortening of the late-corrected QT interval after exposure. Overall, exposures of healthy subjects to EC UFP at these concentrations did not cause clinically important changes in ECG-derived parameters.

One interpretation of these studies is that the cardiovascular effects of $PM_{2.5}$ are seen only in susceptible subgroups of the population. In a study of approximately 500 older men in Boston, long term average $PM_{2.5}$ was associated with decreased HRV, and these associations were stronger among patients with a history of ischemic heart disease, hypertension, and diabetes (Park et al., 2005). In further analyses of these subjects, Schwartz et al. (2005b) found the association between lower high frequency HRV measurements with high $PM_{2.5}$ was reduced in those subjects without the GSTM1 allele (an indication of genetic susceptibility) and those taking statins. Obese patients and patients with high neutrophil counts had increased response to $PM_{2.5}$. This suggests that the effects of $PM_{2.5}$ might be mediated by ROS.

Laboratory Animal Studies: Adult rats exposed by intratracheal instillation of urban air particles or by inhalation of Boston CAPs were evaluated for cardiac dysfunction (Rhoden et al., 2005). HR increased immediately after PM exposure (by instillation or inhalation) but returned to basal levels within 30 min. HRV was unchanged immediately after exposure, but significantly increased during the recovery phase. Pretreatment of the rats with N-acetylcysteine (NAC), a stimulant of glutathione (a powerful antioxidant) production, prior to PM exposure prevented changes in HR and HRV.

Animal studies in the PM Centers have focused on animal models of chronic disease thought to increase susceptibility to PM effects. In spontaneously hypertensive rats, exposure to CAPs caused a decrease in respiratory rate soon after the start of exposure, and stopped when exposure to CAPs ceased (Nadziejko et al., 2002a). The decrease in respiratory rate was accompanied by a decrease in HR.

In Tuxedo, NY, Hwang et al. (2005) found sub-chronic (five month) exposures in the summer of 2003 to CAPs in mice with genetic predisposition to atherosclerotic disease (lacking apoliproprotein, ApoE-/-) produced decreased HR, body temperature, and physical activity (Hwang et al. 2005). No associations were found in normal (C57BL/6) mice. Chen and Hwang (2005) found that the cardiac autonomic function in these ApoE-/- mice was affected by these subchronic CAPs exposures, involving a perturbation of the homeostatic function (parasympathetic/sympathetic balance) in the cardiovascular system (initial enhancement and later depression of the HRV parameters). In a 6-month follow-up subchronic CAPs inhalation study, the $ApoE^{-/-}$ mice were exposed for 6 hours/day to CAPs at an average concentration of 85 $\mu g/m^3$. The av. Ni concentration was 43 ng/m^3 but, on 14 days, there were Ni peaks at ~175 ng/m^3, and unusually low FPM and V. Back-trajectory analyses identified a remote Ni point source.

ECG measurements showed Ni was the only component that was significantly associated with acute changes in HR and HRV (Lippmann et al., 2006).

In Seattle, aged ApoE-/- mice exposed intranasally to saline, local $PM_{2.5}$ or silica (Min-u-Sil 5) showed an initial increase in both HR and activity in all groups, but delayed bradycardia, with no change in activity of the animals in the PM and silica exposed groups. In addition, with PM and silica exposure, there was a decrease in HRV parameters suggesting a decrease in parasympathetic tone, which may lead to cardiac arhythmia (Corey et al., 2005).

In Boston, after exposure to CAPs or filtered air, dogs underwent reversible 5-min coronary artery occlusion (Wellenius et al., 2003). ST-segment elevation during occlusion, a measure of myocardial ischemia, was significantly enhanced following CAPs exposure, compared to filtered air exposures. ST-segment elevation was significantly correlated with crustal elements, possibly associated with urban street dust, but not with CAPs mass or number concentrations. HR was not affected by the CAPs exposures.

Vascular Changes

The observed cardiovascular effects of PM air pollution also may be mediated through vascular changes. Delfino et al. (2005) suggested that UFP may be specifically associated with vascular changes based on PN and surface area.

Population Studies: In cardiac patients undergoing rehabilitation therapy in Boston, ambient $PM_{2.5}$ was associated with increased blood pressure (Zanobetti et al., 2004). A panel study of 88 older healthy or subjects with lung or heart disease in Seattle (Mar et al., 2005) found a small increase in systolic blood pressure associated with $PM_{2.5}$ concentrations in the healthy subjects. In the chamber exposure studies of Gong CAPs exposure among healthy adults, but decreased among asthmatic subjects (Gong et al., 2003). to filtered air or CAPs, systolic blood pressure was modestly increased during CAPs exposure among healthy adults, but decreased among asthmatic subjects.

O'Neill et al. (2005) reported that air pollution in the six days prior to an examination was associated with decreased vascular re-activity, and brachial artery diameter responses among diabetic patients, but not among non-diabetic patients in Boston. Studies in rats (Batalha et al., 2002) and mice (Lemos et al., 2006) showed morphometric measures of vasoconstriction in the lung and heart.

Animal Studies: Exposure of aged male Fischer-344 rats in a mobile laboratory for 6 hours to the traffic aerosol on the New York State Thruway between Rochester and Buffalo resulted in significant increases in plasma endothelin-2, a vasoconstricting protein (Elder et al., 2004). Changes in fibrinogen as an acute phase protein were also observed.

Systemic Inflammation

Population Studies: $PM_{2.5}$ air pollution may also act through increased systemic inflammation. Repeated blood samples of 57 male patients with coronary heart disease from Germany (Ruckerl et al., 2006), found increased C reactive protein, an indicator of acute systemic inflammation, that was associated with $PM_{2.5}$.

In the chamber studies of Gong et al. (2003), systemic effects were assessed in healthy adult and asthmatic volunteers exposed for 2 hours to filtered air or CAPs. Both

groups showed CAPs-related increases in certain blood mediators of inflammation, i.e., soluble intercellular adhesion molecule (ICAM-1) and interleukin-6 (IL-6). However, healthy and asthmatic subjects exposed to EC UFP (~25 nm) for 2 hours with intermittent exercise showed no significant effects on measures of systemic inflammation, including serum amyloid A (SAA), IL-6, and soluble ICAM-1 (Pietropaoli et al., 2004).

Laboratory Animal Studies: Clarke et al. (2000) exposed dogs to CAPs from the Boston area. There was no effect of total PM mass on indicators of systemic inflammation, but factor analysis suggested that specific $PM_{2.5}$ components were associated with inflammatory cell responses (peripheral white blood cell, circulating neutrophils, and circulating lymphocytes) in the blood.

At the end of the third subchronic CAPs inhalation study in Tuxedo, NY in $ApoE^{-/-}$ mice, there were: enhanced vasoconstrictor responses to phenylephrine and serotonin challenge in the thoracic aorta; attenuated relaxation to the endothelium dependent agonist acetylcholine; and marked increases in macrophage infiltration (CD68 Staining), inducible isoform of nitric oxide synthase (iNOS), increased generation of reactive oxygen species, and greater immunostaining for the protein nitration product 3-nitrotyrosine (Sun et al., 2005).

Atherosclerosis

Atherosclerosis is a progressive irreversible condition and an underlying cause of many cardiovascular diseases.

Population Studies: In epidemiologic studies, long-term exposure to $PM_{2.5}$ has been reported to be associated with atherosclerosis measured by carotid intimal media thickness (Kunzli et al., 2005).

Laboratory Animal Studies: Chen and Nadziejko (2005) found that sub-chronic exposure of mice prone to the development of atherosclerotic lesions exposed for five months to CAPs had significantly increased percentage of aortic intimal surface covered by atherosclerotic lesions, and increased plaque cellularity, pointing to PM associated atherosclerosis as a potentially important pathway for the observed cardiovascular effects of long-term $PM_{2.5}$ exposure. In a follow-up study lasting six months, Sun et al. (2005) reported enhanced atherogenesis with accompanied increases in lipid content (ORO staining).

Myocardial Infarction

An association between exposure to vehicular traffic in urban areas and the exacerbation of CVD was suggested in a case-crossover study that was designed to assess whether exposure to traffic effluents can trigger myocardial infarction. Cases of myocardial infarction were identified with the use of data from the Cooperative Health Research in the Region of Augsburg Myocardial Infarction Registry in Augsburg, in southern Germany. (Peters et al., 2004) Subjects that were included had survived for at least 24 hours after the event, completed the registry's standardized interview, and provided information on factors that may have triggered the myocardial infarction. An association was found between exposure to traffic and the onset of a myocardial infarction within one hour afterward (odds ratio, 2.92; 95 percent confidence interval, 2.22 to 3.83; $p<0.001$). The time the subjects spent in cars, on public transportation, or on motorcycles or bicycles was consistently linked with an increase in the risk of myocardial

infarction. Adjusting for the level of exercise on a bicycle or for getting up in the morning changed the estimated effect of exposure to traffic only slightly (odds ratio for myocardial infarction, 2.73; 95 percent confidence interval, 2.06 to 3.61; $p<0.001$). The subject's use of a car was the most common source of exposure to traffic; nevertheless, there was also an association between time spent on public transportation and the onset of a myocardial infarction one hour later. Thus, transient exposure to traffic may increase the risk of myocardial infarction in susceptible persons.

Coagulation Studies

Adverse effects of inhaled PM may be the indirect result of a PM-induced increase in blood coagulability.

Population Studies: Healthy and asthmatic subjects inhaling EC UFP showed no effects of inhalation on measures of coagulation (platelet count, serum fibrinogen, factor VII, or Von Willibrand's factor antigen) in venous blood (Pietropaoli et al., 2004). Thus there is no evidence from the PM Centers for PM acting through this pathway.

Laboratory Animal Studies: Blood samples were collected from healthy rats before, and 0, 6, and 12 hours after 6 hours of exposure to filtered air or CAPs. Prothrombotic changes in blood coagulation parameters (platelet count, fibrinogen level, factor VII activity, thrombin-antithrombin complex [TAT] level, tissue plasminogen activator [tPA] activity, and plasminogen activator inhibitor [PAI] activity) were not associated with CAPS exposures (Nadziejko et al., 2002b).

RESPIRATORY EFFECTS

Since the lungs represent the portal of entry and the first line of defense, early studies focused on the respiratory effects of PM air pollution. Investigations continue into the respiratory health effects of PM, particularly among children with developing lungs and among adults and children with chronic respiratory disease.

Respiratory Mortality and Morbidity

In cause-of-death data in the ACS cohort study (Pope et al., 2004), long-term $PM_{2.5}$ exposures were only weakly associated with respiratory causes of death. Similarly, in the Harvard Six Cities cohort study (Laden et al., 2006), the number of respiratory deaths remained small in the extended follow-up, and their associations with $PM_{2.5}$ were weak, and not statistically significant.

Respiratory mortality was positively associated with PM_{10} exposure on the same and previous two days in an analysis of daily mortality in twenty US cities (Zeka et al., 2005). Respiratory emergency room visits in Spokane were associated with $PM_{2.5}$ but not with the coarse fraction (Slaughter et al., 2005). No association was found with cardiac or respiratory hospital admissions.

Asthma

PM exposures have been associated with acute and chronic respiratory health effects. Recent studies have focused on the effects of PM on the developing respiratory

system of children, and potential associations with the development of asthma. Children living in Southern California exposed to higher levels of PM $PM_{2.5}$ and PM_{10} had reduced rates of growth and reduced attained level of FEV_1 by age 18 (Gauderman et al., 2004). In a study of 208 children in Southern California with NO_2 measured outside their homes, the rates of respiratory illness or asthma were associated with outdoor NO_2 levels and proximity to freeways, suggesting asthma is associated with fresh traffic related air pollutants (Gauderman et al., 2005). This was supported in a survey of 5,341 kindergarten and 1st grade school children in Southern California, which showed residence within 75 m of a major road was associated with increased risk of asthma and wheeze (McConnell et al., 2006).

Air pollution may exacerbate disease and/or decrease lung function in patients with chronic respiratory disease. In a panel of asthmatic children in Southern California, FEV_1 decreased with increasing $PM_{2.5}$ exposures in the prior 24 hours (Delfino et al., 2004). In a panel study of asthmatic adults and children in Spokane, WA, sputum production, runny nose and cough was associated with various measures of PM in the children, but not in adults (Mar et al., 2004). These studies suggest that both coarse and fine particles may aggravate asthma symptoms.

In an analysis of a registry of cystic fibrosis patients across the US, higher average PM air pollution concentrations in their communities was associated with increased risk of pulmonary exacerbations and lower lung function in the cystic fibrosis patients (Goss et al., 2004).

Airway Inflammation

Recent epidemiologic studies and animal and human inhalation studies have shown that short-term ambient $PM_{2.5}$ may have inflammatory effects in the lungs.

In panels of elderly subjects, ambient $PM_{2.5}$ was associated with increased exhaled NO (Adamkiewicz et al., 2004), an indicator of inflammation in the lungs. Koenig et al. (2005) found exhaled NO was associated with personal exposures to ambient outdoor PM, but not to indoor generated PM.

In the human clinical studies, Ghio et al. (2000) found modest increases in inflammatory cells in bronchoalveolar lavage fluid from healthy subjects after inhalation of CAPs from the Chapel Hill, NC area. In contrast, Gong et al. (2004) found no increases in inflammatory cells in induced sputum or changes in pulmonary function following $PM_{2.5}$ CAPs inhalation, in young healthy or asthmatic subjects or in healthy elderly or subjects with COPD. Similarly, no inflammatory effects were observed with exposures to CTPM (Gong et al., 2004).

Pietropaoli et al. (2004) exposed subjects to 10 to 25 $\mu g/m^3$ EC UFP for 2 hours, with intermittent exercise. They found no effects on sputum inflammatory cells, pulmonary function, or exhaled NO. Additional studies at 50 $\mu g/m^3$ also showed no changes in pulmonary function or exhaled NO.

Clarke et al. (2000) exposed dogs to CAPs from the Boston area. There was no effect of total PM mass on indicators of airway inflammation, but factor analysis suggested that specific PM components were associated with specific inflammatory cell responses in the lung.

Pulmonary Vascular Effects

PM exposure may cause pulmonary vasoconstriction. In randomized, double-blind studies, healthy and asthmatic subjects exposed to EC UFP (50 $\mu g/m^3$) showed decreased pulmonary diffusing capacity for CO at 21 hours after exposure, a finding consistent with decreased pulmonary capillary blood volume in response to UFP (Frampton et al., 2006).

NERVOUS SYSTEM EFFECTS

Effects of ambient air PM on the nervous system were produced in $ApoE^{-/-}$ mice undergoing six months of 30 hr/wk subchronic CAPs inhalation exposures in Tuxedo, NY at an av. concentration of 110 $\mu g/m^3$. This strain of mice has elevated oxidative stress in the brain. At the end of the exposure sequence, the neurons from the substantia nigral nucleus compacta were significantly reduced (29%) as compared to the sham-exposed mice, and there was a significant increase in immunocytochemically stained astrocytes (Veronesi et al., 2005). Gene expression analyses on these mice (Gunnison and Chen, 2005) showed exposure-related changes indicative of alteration in circadian rhythm that could be related to the changes in the brain. These unanticipated changes associated with subchronic CAPs inhalation exposures at environmentally relevant concentrations indicate a need for further research on the effects of $PM_{2.5}$ on the central nervous system.

Inhalation by rats of EC UFP using ^{13}C for six hours showed significant and persistent increases of ^{13}C in the olfactory bulbs over 1 to 7 days post-exposure, with other brain regions showing no or less and inconsistent increases (Oberdörster et al., 2004). The authors attributed this to a direct access of the inhaled UFP to the CNS from deposits in the nose *via* the olfactory nerve.

CONCLUSIONS

The research conducted at the EPA PM Centers on health effects has provided a substantial body of support for the recent associations between ambient $PM_{2.5}$ and cardiovascular disease exacerbation. The potential pathophysiological changes identified include an induction of systemic inflammation and the exacerbation of atherosclerosis, as well as alteration in the autonomous nervous system control and induction of cardiac arrhythmia. These changes are consistent with the increased risk of hospitalization due to myocardial infarctions, congestive heart failure and ischemic stroke. However, considerable heterogeneity was observed comparing $PM_{2.5}$ at different locations as well as study different population subgroups, indicating that the underlying biological mechanisms have not been completely unraveled. Concurrently, PM Center research has helped to clarify: 1) the role of chronic $PM_{2.5}$ exposure on respiratory disease-related mortality and lung function growth in children; and 2) the effects of short-term peak exposures to $PM_{2.5}$ on airway inflammation. It has also indicated that repeated $PM_{2.5}$ exposure can result in the loss of cells in the brain and that inhaled UFP can translocate *via* sensory neurons to the brain.

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