



Health Effects of Particulate Air Pollution

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This report compiles and summarizes recent studies and research programs that have been conducted on the effects of air pollution particulate matter on human health.

Executive Summary

PM Effects on Respiratory and Cardiovascular Systems

- [Study Finds Black Carbon Linked to Increased Cardiovascular Risk \(p.2\)](#)
- [A Systematic Review and Meta-Analysis of Outdoor Particulate Matter Exposure and Lung Cancer \(p. 3\)](#)
- [Exposure to Particulate Pollution Associated With Lung Cancer \(p. 3\)](#)
- [HEI Publishes Two Comprehensive Studies on Health Effects of PM \(p. 4\)](#)
- [China Study Shows PM1 Air Pollution Most Harmful \(p. 5\)](#)
- [Air Pollution Linked With Thickening of the Arteries, Cardiovascular Problems \(p. 6\)](#)
- [Detailed diesel exhaust characteristics including particle surface area and lung deposited dose for better understanding of health effects in human chamber exposure studies \(p. 7\)](#)
- [Study Finds Increasing Emergency Room Visits for Stroke by Elevated Levels of Fine Particulate Constituents \(p. 8\)](#)
- [Cell Cycle Alterations Induced by Urban PM2.5 in Bronchial Epithelial Cells \(p. 8\)](#)
- [Air Pollution and Hospital Emergency Room and Admissions for Cardiovascular and Respiratory Diseases in Dona Ana County, New Mexico \(p. 9\)](#)
- [A Case-Crossover Study on Ambient Fine Particulate Air Pollution Triggers ST-Elevation Myocardial Infarction \(p. 9\)](#)
- [Study Associates Air Pollution to Irregular Heartbeat and Lung Blood Clots \(p. 10\)](#)
- [Study Finds Living in Areas Polluted with Fine Particles Raises Lung Cancer Risk \(p. 11\)](#)
- [Increased Ultrafine Particles and Carbon Monoxide Concentrations Are Associated with Asthma Exacerbation Among Urban Children \(p. 12\)](#)
- [New Study Finds Strong Association between Exposure to Fine PM and Cardiovascular Mortality \(p. 13\)](#)
- [Effects of Concentrated Ambient Particles on Normal and Hypersecretory Airways in Rats \(p. 13\)](#)
- [WHO Releases Report on Health Effects of PM \(p. 15\)](#)

Ultrafine PM

- [Researchers Publish Study on PM2.5 Constituents and Hospital Visits in Shanghai \(p. 15\)](#)
- [Epidemiological Evidence on Human Effects of Ultrafine Particles \(p. 16\)](#)
- [HEI Releases New Report on Health Effects of Ultrafine Particles \(p. 16\)](#)
- [Study Identifies Toxicity of Fine and Ultrafine PM from Specific Sources \(p. 17\)](#)
- [Predicting Primary PM2.5 and PM0.1 Trace Composition for Epidemiological Studies in California \(p. 18\)](#)
- [Researchers find Ultrafine Particles Have Independent Health Impacts from Larger Particles \(p. 19\)](#)

PM and Premature Mortality

- [SCAQMD Releases Latest Air Toxics Study, Concludes 57% Drop in Cancer Risk Since 2005 \(p. 19\)](#)
- [NASA Map Shows Deadliest Places on Earth Associated with PM2.5 Air Pollution \(p. 20\)](#)

Executive Summary (continued)

- [New Study Finds Association Between Reductions in PM_{2.5} Levels and Improved Life Expectancy in U.S. \(p. 21\)](#)
- [EPA Research Finds Exposure to Ozone and PM_{2.5} Can Lead to Premature Death \(p. 21\)](#)
- [Modeling Source-Attributable Health Impacts of Ambient Particulate Matter Exposure: Global Premature Mortality from Surface Transportation Emissions in 2005 \(p. 22\)](#)

PM Effects on Cognitive and Neurological Functions

- [Study Warns on Possible Air Pollution Link to Neuroinflammatory, Alzheimer and Parkinson's Pathologies in Children \(p. 23\)](#)
- [Study Links PM_{2.5} Exposure to Physical Changes in Brain \(p. 23\)](#)
- [Neurotoxicity of Traffic-related PM on Human Brain Structure \(p. 24\)](#)
- [Exposure to Vehicle Emissions Results in Altered Blood Brain Barrier Permeability and Expression of Matrix Metalloproteinases and Tight Junction Proteins in Mice \(p. 25\)](#)
- [New Study Finds Air Pollution Linked to Cognitive Decline in Later Years \(p. 26\)](#)
- [Study Links PM Air Pollution to Autism, Schizophrenia \(p. 27\)](#)
- [Associations between Traffic-Related Black Carbon Exposure and Attention in a Prospective Birth Cohort of Urban Children \(p. 27\)](#)
- [Convergence of Human, Animal, and *In Vitro* Studies on the Effects of Air Pollution on the Brain \(p. 28\)](#)

PM Effects on Human Reproduction

- [New Study Concludes that Carbon Nanoparticles in PM_{2.5} Can Lead to Miscarriage \(p. 29\)](#)
- [Study Finds Air Pollution Exposure in Second Trimester May Increase Asthma Risk in Children \(p.29\)](#)
- [Adverse Reproductive Health Outcomes and Exposures to Gaseous and Particle Matter Air Pollution in Pregnant Women \(p. 30\)](#)

PM from Alternative Fuels

- [Study Reports that Biodiesel PM May Have Greater Adverse Health Effects Than Diesel \(p. 31\)](#)
- [Study Characterizes PM Toxicity from Diesel Passenger Cars Using DPF and Biodiesel Fuel \(p. 32\)](#)
- [Characteristics of Particulate Matter Emissions from a Current Technology Natural Gas Engine \(p. 33\)](#)

U.S. EPA and California ARB Funded Research Projects on the Health Effects of PM

- [U.S. EPA Clean Air Research Centers Awarded Funding to Investigate Health Effects of Air Pollution \(p. 33\)](#)

PM EFFECTS ON RESPIRATORY AND CARDIOVASCULAR SYSTEMS

Study Finds Black Carbon Linked to Increased Cardiovascular Risk—According to a new international study led by McGill University Professor Jill Baumgartner, black carbon (BC) from incomplete biomass and fossil fuel combustion is the most strongly light-absorbing component of particulate matter air pollution and a major climate-forcing emission. The study suggests that BC may also increase the risk of cardiovascular disease. The team's findings are published in the August 2014 *Proceedings of the National Academy of Sciences of the United States* (PNAS).

China's PM air pollution significantly exceeds health guidelines and is driven by industrial emissions, motor vehicles, and household use of biomass and coal fuels. Baumgartner and her colleagues measured the daily exposure to different types of air pollutants, including black carbon, in 280 women (mean age 51.9 years) in China's rural Yunnan province, where biomass fuels are commonly used. They found that BC exposure from biomass smoke is more strongly associated with blood pressure, which directly impacts cardiovascular risk, than total PM mass, and that co-exposure to motor vehicle emissions may strengthen BC's impact. Air

pollution mitigation efforts focusing on reducing combustion pollution are likely to have major benefits for climate and human health.

The researchers outfitted women with wearable air samplers that collected fine particulate matter. The particulate samples were then analyzed for different pollutant types, including black carbon. The women's blood pressure, salt intake, physical activity, body mass index, and their proximity to highways were also measured.

In addition, the researchers found that women living closer to highways and exposed to both wood smoke and traffic emissions had three times higher blood pressure than women who lived away from highways. BC had the strongest association with systolic blood pressure (SBP), followed by PM mass and water-soluble organic mass. The team also found that effect of BC on SBP was almost three times greater in women living near the highway.

More information on this is available at:

<https://www.mcgill.ca/newsroom/channels/news/black-carbon-linked-risk-cardiovascular-disease-238419>.

A Systematic Review and Meta-Analysis of Outdoor Particulate Matter Exposure and Lung Cancer—Particulate matter in outdoor air pollution was recently designated a Group 1 carcinogen by the International Agency for Research on Cancer (IARC). This determination was based on the evidence regarding the relationship of PM_{2.5} and PM₁₀ to lung cancer risks. However, the IARC evaluation did not include a quantitative summary of the evidence. The goal of this review was to provide a systematic review and quantitative summary of the evidence regarding the relationship between PM and lung cancer.

The researchers conducted a meta-analysis of studies examining the relationship of exposure to PM_{2.5} and PM₁₀ with lung cancer, incidence and mortality. In total, 18 studies met their inclusion criteria and provided the information necessary to estimate the change in lung cancer risk per 10 µg/m³ increase in exposure to PM. They used random-effects analyses to allow between-study variability to contribute to meta-estimates.

The results of these analyses, and the decision of the IARC Working Group to classify outdoor air pollution as a Group 1 carcinogen, further justify efforts to reduce exposures to air pollutants, which can arise from many sources. The Global Burden of Disease collaboration estimated that approximately 3.22 million deaths were caused by exposure to air pollution in 2010, an increase from 2.91 million deaths attributed to air pollution in 1990. Cancers of the trachea, bronchus, or lung represent approximately 7% of total mortality attributable to PM_{2.5} in 2010. The results of the meta-analysis provided in this study could be useful for better quantifying the burden of lung cancer associated with air pollution.

A copy of the study, published in *Environmental Health Perspectives* in September 2014 is available at: <http://ehp.niehs.nih.gov/wp-content/uploads/122/9/ehp.1408092.pdf>.

Exposure to Particulate Pollution Associated With Lung Cancer – Exposure to particulate air pollution is associated with lung cancer incidence, according to a prospective

analysis of data from 17 European cohort studies. Researchers set out to assess the association between long-term exposure to ambient air pollution and lung cancer incidence across nine European countries. This study, Prospective Analyses from the European Study of Cohorts for Air Pollution Effects (ESCAPE), was published in the journal *Lancet Oncology* in August 2013.

Air pollution was assessed by land-use regression models for particulate matter of less than 10 μm , less than 2.5 μm , and between 2.5 μm and 10 μm , as well as nitrogen oxides, soot and two traffic indicators. The 312,944 people included in the analysis equated to 4,013,131 person-years at risk. Within the 12.8-years follow-up, there were 2,095 cases of incident lung cancer. A significant association was found between lung cancer risk and exposure to particulate matter of less than 10 μm (HR=1.22; 95% CI, 1.03–1.45); the HR for particulate matter of less than 2.5 μm was 1.18 (95% CI, 0.96-1.46). The HR for the association between adenocarcinomas and exposure to particulate matter of less than 10 μm was 1.51 (95% CI, 1.10-2.08), and the HR for association between adenocarcinomas and exposure to particulate matter of less than 2.5 μm was 1.55 (95% CI, 1.05-2.29).

Researchers reported no association between lung cancer and nitrogen oxide concentration (HR=1.01; 95% CI, 0.95–1.07) or traffic intensity on the nearest street (HR= 1.00; 95% CI, 0.97–1.04).

Researchers noted the study may have been limited because data for previous lung disease were not obtained. “Previous lung disease might be associated with both air pollution concentrations and the risk for lung cancer,” they wrote. In an accompanying editorial, Takashi Yorifuji, MD, of the department of human ecology at Okayama University Graduate School of Environmental and Life Science in Japan, and Saori Kashima, PhD, of the department of public health and health policy at the Institute of Biomedical and Health Sciences at Hiroshima University in Japan, wrote: “At this stage, we might have to add air pollution, even at current concentrations, to the list of causes of lung cancer and recognize that air pollution has large effects on public health ... Fortunately, like tobacco smoking, it is a controllable factor.” The study was funded by the European Community’s Seventh Framework Program.

More information on this is available at: <http://www.ncbi.nlm.nih.gov/pubmed/23849838>.

HEI Publishes Two Comprehensive Studies on Health Effects of PM – In October 2013, the Health Effects Institute (HEI) published two new comprehensive studies on the health effects of PM and its components. Despite previous claims that certain sources of fine PM air pollution (PM_{2.5}) may be less toxic than others, the results of the two studies lead to the overall conclusion that no source can yet be excluded as having no health effects. These nationwide studies, funded as part of HEI’s National Particle Component Toxicity (NPACT) initiative, are the most systematic effort ever to combine epidemiologic and toxicologic research to investigate whether “all particles are created equal” and therefore deserve the same level of public health and regulatory attention.

The studies found links between adverse health effects, particularly on the cardiovascular system, and sulfate particles (primarily from coal combustion) and, to a somewhat lesser extent,

traffic sources. But the HEI NPACT Review Panel, 14 experts who subjected the studies to intense, independent peer review, cautioned that the results “do not provide compelling evidence that any specific source, component, or size class of PM may be excluded as a possible contributor to PM toxicity.” The panel went on to note that a “better understanding of exposure and health effects is needed before it can be concluded that regulations targeting specific sources or components of PM_{2.5} will protect public health more effectively than continuing to follow the current practice of targeting PM_{2.5} mass as a whole.”

HEI launched the NPACT initiative in response to calls from its sponsors, at both the U.S. EPA and industry, for answers to these important questions about PM and health. Following extensive planning and intense scientific competition, two teams, led by Morton Lippmann from New York University and Sverre Vedal from the University of Washington-Seattle, were selected to conduct detailed toxicologic and epidemiologic investigations across the U.S. of air pollution and its effects on cardiovascular and other health outcomes.

Lippmann and colleagues conducted four coordinated toxicologic and epidemiologic studies. They analyzed heart rate variability and atherosclerosis as well as markers of inflammation and oxidative stress in animals and human cells exposed to PM samples from five geographic regions in the U.S. In epidemiologic studies, they examined short-term effects on mortality and hospital admissions associated with PM_{2.5} emission in 150 U.S. cities; they also evaluated associations between long-term exposure to PM and mortality from cardiovascular and respiratory diseases and lung cancer for participants in the American Cancer Society’s Cancer Prevention Study population. Their study has provided new insights into the toxicity of PM components and source categories and identified the coal combustion, residual oil combustion, traffic, and metals source categories as most consistently associated with adverse health effects. However, other components and source categories could not be definitively excluded as having no adverse effects.

Vedal and colleagues studied the cardiovascular effects of PM components, with a focus on traffic sources. They analyzed data from the Multi-Ethnic Study of Atherosclerosis and the Women’s Health Initiative Observational Study cohorts, and they also exposed mice to combinations of mixed vehicular engine emissions and non-vehicular PM. They found strong evidence for associations of PM_{2.5}, organic carbon, and sulfur with subclinical and clinical outcomes in the cohorts, with weaker evidence for elemental carbon. Their toxicologic study provides strong evidence for effects of mixed vehicular engine emissions and, to a lesser extent, exhaust gases on vascular markers in mice; non-vehicular PM induced few effects.

For a copy of the press release announcing the two NPACT studies, go to: www.healtheffects.org/Pubs/HEI-NPACT-PressRelease-October-30-2013.pdf. An executive summary of the two studies is available at: www.healtheffects.org/Pubs/NPACT-ExecutiveSummary.pdf.

China Study Shows PM₁ Air Pollution Most Harmful – A recent study led by Chinese scientists shows a strong link between smaller air pollution particles and a range of serious health conditions. Scientists said the smaller the airborne particles, the more likely they are to cause illness, suggesting the need for monitoring particulate matter of 1 micron or less in diameter, a

category of pollution rarely monitored. In recent years, many locations across China have been blanketed with heavy air pollution, raising public health concerns.

In the study, published in the public health journal *Environmental Health Perspectives* in October 2013, researchers from the School of Public Health at Fudan University in Shanghai have demonstrated correlations between PM_{2.5} pollution and the incidence of particular illnesses. Researchers spent about two years collecting data in a medium-sized city in northern China, measuring levels of PM in 23 size categories ranging from 0.25 microns to 10 microns. They then plotted the health conditions of residents in the city against the concentrations of particles of different sizes found in their locations.

Among the key findings was that those areas with larger concentrations of smaller particles showed higher incidences of particular illnesses, such as cardiovascular diseases. The fine particles measuring between 0.25 to 0.5 microns in diameter accounted for about 90% of the total number of particles found in the air during the study. Kan Haidong, a professor at the School of Public Health at Fudan University, said the smaller the particle, the higher the concentration in any given volume of air and so the greater the number of particles coming into contact with tissues inside the body. Kan said the smaller particles can also pass through the blood-air barrier in the lungs, entering the blood as toxins, and causing cardiovascular disease. He also said that smaller particles in the body can harm the regulation of the human nervous system.

More information on this is available at: usa.chinadaily.com.cn/china/2013-10/28/content_17061997.htm.

Air Pollution Linked With Thickening of the Arteries, Cardiovascular Problems – Air pollution has been linked to heart attacks, strokes and atherosclerosis ("hardening of the arteries"), thanks to research published in *PLOS Medicine* in April 2013. The study found that high concentrations of fine particulate air pollution (PM_{2.5}) were linked with faster thickening of artery walls. The thickening was found in the inner walls of the carotid artery. This is the main blood vessel providing blood to the head, neck and brain.

The team also found that reductions in particulate levels were linked to a slower progression of blood vessel thickness. Blood vessel thickness is a symptom of atherosclerosis, and is present throughout the body even for people without obvious symptoms of heart disease. "Our findings help us to understand how it is that exposures to air pollution may cause the increases in heart attacks and strokes observed by other studies," said Sara Adar, John Searle Assistant Professor of Epidemiology, University of Michigan School of Public Health. The research was conducted by a team led by Adar and Joel Kaufman, Professor of Environmental and Occupational Health Sciences and Medicine, University of Washington. The researchers investigated 5362 people aged between 45 to 84 years old from six U.S. metropolitan areas as part of the Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air). They took ultrasound measurements of blood vessels 3 years apart. All participants in the study had no known heart disease. The researchers found that on average, the thickness of the carotid vessel increased by 14 μm each year. Thickening of the inner two layers of this key blood vessel, which supplies blood to the head, neck and brain, occurred more quickly following exposure to higher

concentrations of fine particulate air pollution. The researchers said the thickness of the carotid artery is an indicator of how much atherosclerosis is present in the arteries throughout the body. "Linking these findings with other results from the same population suggests that persons living in a more polluted part of town may have a 2 percent higher risk of stroke as compared to people in a less polluted part of the same metropolitan area," Adar said. In response to the findings, Nino Kuenzli, of the University of Basel in Switzerland, said in a news release that the study "further supports an old request to policy makers -- namely that clean air standards ought to comply at least with the science-based levels proposed by the World Health Organization."

More information on this is available at:

<http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001430>.

Detailed diesel exhaust characteristics including particle surface area and lung deposited dose for better understanding of health effects in human chamber exposure studies – Several diesel exhaust (DE) characteristics, comprising both particle and gas phase, recognized as important when linking with health effects, are not reported in human chamber exposure studies. In order to understand effects of DE on humans there is a need for better characterization of DE when performing exposure studies. This study, published in *Atmospheric Environment* in April 2014, aims to determine and quantify detailed DE characteristics during human chamber exposure.

Additionally to compare to reported DE properties in conducted human exposures. A wide battery of particle and gas phase measurement techniques have been used to provide detailed DE characteristics including the DE particles (DEP) surface area, fraction and dose deposited in the lungs, chemical composition of both particle and gas phase such as NO, NO₂, CO, CO₂, volatile organic compounds (including aldehydes, benzene, toluene) and polycyclic aromatic hydrocarbons (PAHs). Eyes, nose and throat irritation effects were determined. Exposure conditions with PM₁ (<1 μm) mass concentration 280 μg m⁻³, number concentration 4 × 10⁵ cm⁻³ and elemental to total carbon fraction of 82% were generated from a diesel vehicle at idling. When estimating the lung deposited dose it was found that using the size dependent effective density (in contrast to assuming unity density) reduced the estimated respiratory dose by 132% by mass. Accounting for agglomerated structure of DEP prevented underestimation of lung deposited dose by surface area by 37% in comparison to assuming spherical particles. Comparison of DE characteristics reported in conducted chamber exposures showed that DE properties vary to a great extent under the same DEP mass concentration and engine load. This highlights the need for detailed and standardized approach for measuring and reporting of DE properties. Eyes irritation effects, most probably caused by aldehydes in the gas phase, as well as nose irritation were observed at exposure levels below current occupational exposure limit values given for exhaust fumes. Reporting detailed DE characteristics that include DEP properties (such as mass and number concentration, size resolved information, surface area, chemical composition, lung deposited dose by number, mass and surface) and detailed gas phase including components known for their carcinogenic and irritation effect (e.g. aldehydes, benzene, PAHs) can help in determination of key parameters responsible for observed health effects and comparison of chamber exposure studies.

More information on this is available at:
<http://www.sciencedirect.com/science/article/pii/S1352231013008546>.

Study Finds Increasing Emergency Room Visits for Stroke by Elevated Levels of Fine Particulate Constituents – The association between PM_{2.5} and stroke remain inconsistent. Researchers conducted a time-series study to evaluate emergency room visits for ischemic and hemorrhagic stroke in relation to PM_{2.5} and its constituents. Generalized additive models were used to model the counts of daily ER visits for ischemic and hemorrhagic strokes among patients admitted to the National Taiwan University Hospital from January 1, 2004 to August 31, 2008. Exposure variables included PM_{2.5} and the four constituents, nitrate, sulfate, organic carbon (OC), and elemental carbon (EC). 12,982 ischemic stroke and 3,362 hemorrhagic stroke cases were identified during the study period. For hemorrhagic stroke, the strongest relative risks (RRs) of ER visits were 1.19 for an interquartile range (IQR) increase in 3-day average nitrate and EC. For ischemic stroke, increased RRs of ER visit of 1.21 and 1.81 were observed in the warm season for an IQR increase in 3-day average of OC and EC, respectively. PM_{2.5} and OC were associated with increased RRs of ER visits for ischemic stroke among patients aged 65 years or older and female patients.

The researchers concluded that PM_{2.5} constituents, rather than PM_{2.5} mass, are more closely related to ER visits for hemorrhagic stroke. Both PM_{2.5} mass and its chemical constituents are associated with ER visits for ischemic stroke in the warm season, among patients older than 65 years, and female patients.

A copy of the study, *Increasing Emergency Room Visits for Stroke by Elevated Levels of Fine Particulate Constituents* published in March 2014, is available for purchase at:
<http://www.sciencedirect.com/science/article/pii/S0048969713014897>.

Cell Cycle Alterations Induced by Urban PM_{2.5} in Bronchial Epithelial Cells – This study explores and characterizes cell cycle alterations induced by urban PM_{2.5} in the human epithelial cell line BEAS-2B, and elucidates possible mechanisms involved.

In October 2013, the International Agency for Research on Cancer (IARC) classified outdoor air pollution as carcinogenic to humans. PM is a well-known air pollutant and its adverse effects on human health are well established. Increased levels of PM have been associated with exacerbation of airways disease in patients with asthma and Chronic Obstructive Pulmonary Disease (COPD). There is a growing evidence linking long-term exposure to fine PM fraction with increased risk of cardiovascular mortality and lung cancer. However, the understanding of the mechanisms by which PM exerts its various adverse effects is still incomplete and detailed *in vitro* studies are highly needed.

In vitro studies have demonstrated that PM may inhibit cell growth, by reducing proliferation and/or causing cell death. The reduced proliferation has been linked to an arrest in various steps of the cell cycle. Cell cycle progression can be blocked and/or delayed in response to various genotoxic stresses, but also to structural dysfunctions of various proteins.

Researchers have observed that exposure to 25 µg/cm² of Milan winter PM_{2.5} for 20 hours induced a mitotic arrest resulting in cell death by apoptosis in human bronchial epithelial

cells. Effects involved in DNA-damaged response were detected at the low doses 5 and 7.5 $\mu\text{g}/\text{cm}^2$. A further characterization of PM-induced cell cycle and mitotic alterations is important when trying to explain PM-induced chromosomal alterations, as well as its association with an increased risk of lung cancer.

In this study, the effects of Milan winter PM_{2.5} on the cell cycle progression were characterized using the low dose 7.2 $\mu\text{g}/\text{cm}^2$. The cells were exposed to a low dose (7.5 $\mu\text{g}/\text{cm}^2$) of PM_{2.5} for different time points, and the cell cycle progression was analyzed by fluorescent microscopy and flow cytometry.

The researchers concluded that Milan winter PM_{2.5} rapidly induces severe cell alterations, resulting in increased frequency of cells with double nuclei and micronuclei. This effect is related to the metabolic activation of PM_{2.5} organic chemicals, which cause damages to DNA and spindle apparatus.

This study was published in the journal *Particle and Fibre Toxicology* in December 2013. More information on this study is available at:
<http://www.particleandfibretoxicology.com/content/10/1/63>.

Air Pollution and Hospital Emergency Room and Admissions for Cardiovascular and Respiratory Diseases in Dona Ana County, New Mexico – Dona Ana County in New Mexico regularly experiences severe air pollution episodes associated with windblown dust and fires. Residents of Hispanic/Latino origin constitute the largest population group in the region. Researchers investigated the associations of ambient PM and ozone with hospital emergency room and admissions for respiratory and cardiovascular visits in adults. The researchers used trajectories regression analysis to determine the local and regional components of particle mass and ozone.

The researchers found that the sources within 500 km of the study area accounted for most of particle mass and ozone concentrations. Sources in Southeast Texas, Baja California and Southwest U.S. were the most important regional contributors. Increases of cardiovascular emergency room visits were estimated for PM₁₀ and PM_{10-2.5} for all adults during the warm period (April to September). When high PM₁₀ mass concentrations were excluded, strong effects for respiratory emergency room visits for both PM₁₀ and PM_{2.5} were computed.

The analysis indicated effects of PM₁₀, PM_{2.5} and ozone on emergency room visits during the April to September period in a region impacted by windblown dust and wildfires.

This study was published in *Environmental Research* in February 2014. More information on this study is available at:
<http://www.sciencedirect.com/science/article/pii/S0013935113002077>.

A Case-Crossover Study on Ambient Fine Particulate Air Pollution Triggers ST-Elevation Myocardial Infarction – Previous studies investigating triggering of myocardial infarction by PM concentrations have, in most cases, reported an increased risk of myocardial infarction associated with increases in PM on the same and previous day. Similar acute effects

of fine particulate air pollution have been reported for other cardiovascular outcomes. Some studies of myocardial infarction and PM have used symptom onset time, rather than the arrival time at the emergency room, to define myocardial infarction onset, thereby providing a better estimate of the myocardial infarction onset time and less exposure error.

Using hospital admissions data, researchers reported that myocardial infarction/PM_{2.5} association may be limited to transmural infarctions. The researchers found a 10% increase risk of transmural infarction, but not non-transmural infarctions associated with each 10.8% $\mu\text{g}/\text{m}^3$ increase in the PM_{2.5} concentration in the preceding 24 hours. The researchers hypothesized that this may be due to differences in response to air pollution by myocardial infarction type. However, transmural and non-transmural myocardial infarction are estimations of assumed injury to the myocardium, whereas acute coronary syndromes attempt to describe the spectrum of physiologic events occurring in coronary arteries during an acute ischemic event. Therefore, in order to better understand the relationship between the acute pathophysiologic process of myocardial infarction and increased air pollutant concentrations, researchers sought to study acute coronary syndromes (i.e. ST segment elevation myocardial infarction [STEMI], non-ST segment elevation myocardial infarction [NSTEMI], and unstable angina) to reflect the spectrum of pathophysiologic events occurring. STEMI is most often the result of plaque rupture followed by thrombus formation and coronary artery lumen occlusion.

The researchers found a significant 18% increase in the risk of STEMI associated with each 7.1 $\mu\text{g}/\text{m}^3$ increase in PM_{2.5} concentration in the previous hour prior to acute coronary syndrome onset, with smaller, non-significantly increased risks associated with increased fine particle concentrations in the previous 3, 12, and 24 hours. The researchers found no pattern with NSTEMI. Estimates of the risk of STEMI associated with interquartile range increases in ultrafine particle and accumulation mode particle number concentrations in the previous 1 to 96 hours were all greater than 1.0, but not statistically significant. Patients with pre-existing hypertension had a significantly greater risk of STEMI associated with increased fine particle concentration in the previous hour than patients without hypertension.

Researchers concluded that increased fine particle concentrations in the hour prior to acute coronary syndrome onset were associated with an increased risk of STEMI, but not NSTEMI. Patients with pre-existing hypertension and other cardiovascular disease appeared particularly susceptible. Further investigation into mechanisms by which PM can preferentially trigger STEMI over NSTEMI within this rapid time scale is needed.

This study was published in the journal *Particle and Fibre Toxicology* in January 2014. More information on this is available at: <http://www.particleandfibretoxicology.com/content/11/1/1>.

Study Associates Air Pollution to Irregular Heartbeat and Lung Blood Clots – A new study linked air pollution to irregular heartbeat and lung blood clots. But its impact on directly boosting the risk of heart attacks and stroke is rather less clear. The evidence suggests that high levels of certain air pollutants are associated with a higher risk of cardiovascular problems, but exactly how this association works has not been clarified.

The research team set out to explore the short-term biological impact of air pollution on cardiovascular disease, using data from three national collections in England and Wales for the 2003-2009 period. These were the Myocardial Ischaemia National Audit Project (MINAP), which tracks hospital admissions for heart attack/stroke; hospital episode statistics (HES) on emergency admissions; and figures from the Office of National Statistics (ONS) on recorded deaths. Some 400,000 heart attacks recorded in MINAP; more than 2 million emergency admissions for cardiovascular problems; and 600,000 deaths from a heart attack/stroke were linked to average levels of air pollutants over a period of 5 days using data from the monitoring station nearest to the place of residence. Air pollutants include carbon monoxide, nitrogen dioxide, particulate matter (PM10 and PM2.5) sulfur dioxide, and ozone. Information on ambient daily temperatures, recorded by the UK Meteorological Office, was also factored in.

No clear link with any air pollutant was found for cardiovascular deaths, with the exception of PM2.5 which was linked to an increased risk of irregular heart rhythms, irregular heartbeat and blood clots in the lungs. Only nitrogen dioxide was linked to an increased risk of a hospital admission for cardiovascular problems, including heart failure, and an increased risk of a particular type of heart attack in the MINAP data. However, there does not seem to be a clear link between PM levels and heightened risk of atrial fibrillation and pulmonary embolism.

This study was published in the *BJM British Medical Journal* in June 2014. More information on this is available at:

<http://www.sciencedaily.com/releases/2014/06/140604203052.htm>.

Study Finds Living in Areas Polluted with Fine Particles Raises Lung Cancer Risk –

A new research concludes that nonsmoking women who live many years in communities polluted with fine particles have an elevated risk of lung cancer. The study, which is the largest to date to examine the link, adds to mounting evidence that chronic exposure to soot may raise the risk of lung cancer, particularly among nonsmokers. Led by Harvard University researchers, the study estimated exposures of 103,650 U.S. women to three sizes of airborne particulates. They calculated how many women contracted cancer (2,155) between 1994 and 2010, and analyzed the pollution levels near their homes for the previous six years.

All sizes of particle pollution, particularly the smallest (PM2.5), were linked to an increased risk of lung cancer. For every small (10 µg/m³) increase in PM2.5 the risk of lung cancer increased 37% among nonsmoking women or women who had quit smoking at least 10 years earlier, which was published online in the journal *Environmental Health Perspectives*. The sources of the pollutants varied. Although the research suggested that traffic played a role in the higher cancer risk, the finding was not scientifically significant because too few women in the study lived near major roads. According to the American Lung Association, more than 46 million Americans, or almost 15%, live in areas with unhealthy year-round levels of fine particle pollution. U.S. areas with the highest levels include the Los Angeles region, California's Central Valley, Chicago and Houston. In this study, about half of the women lived in the Northeast.

The research doesn't prove air pollution causes lung cancer. But it is the latest of multiple human health studies that have linked fine particles to lung cancer. Such studies

prompted the International Agency for Research on Cancer to classify PM as carcinogenic to humans in 2013. The researchers didn't have personal exposure for the women. Instead, they estimated their exposures by plugging local air quality data into models that took into account how close the women lived to major roads, as well as nearby industries and weather conditions.

Edelman of the American Lung Association said the study's strength was that it looked at a period of six years of exposure instead of a snapshot in time. However, one researcher said the study didn't look far enough back in the women's past. Previous exposures may be more important because cancer can develop over a period of decades. The study uses "more or less current exposure to categorize long-term response," said Fred Lipfert, an environmental engineer formerly of the Brookhaven National Laboratory who has published multiple articles on air pollution and health. The other problem is that the study doesn't take into consideration indoor air pollution. Laden agreed that past exposures are important, but the scientists were limited by the data. PM were not routinely measured a decade or two ago.

A copy of the study, published in the *Environmental Health Perspectives* in June 2014, is available at: <http://ehp.niehs.nih.gov/wp-content/uploads/advpub/2014/6/ehp.1307490.pdf>.

Increased Ultrafine Particles and Carbon Monoxide Concentrations Are Associated with Asthma Exacerbation Among Urban Children – Increased air pollution concentrations have been linked to several asthma-related outcomes in children, including respiratory symptoms, medication use, and hospital visits. However, few studies have examined effects of ultrafine particles in a pediatric population. This study's primary objective was to examine the effects of ambient concentrations of ultrafine particles on asthma exacerbation among urban children and determine whether consistent treatment with inhaled corticosteroids could attenuate these effects. The researchers also explored the relationship between asthma exacerbation and ambient concentrations of accumulation mode particles, fine particles (PM_{2.5}), carbon monoxide, sulfur dioxide and ozone. The researchers hypothesized that increased 1-7 day concentrations of ultrafine particles and other pollutants would be attenuated among children receiving school-based corticosteroid therapy.

The researchers conducted a pilot study using data from 3 to 10 year old children participating in the School-Based Asthma Therapy trial. Using a time-stratified case-crossover design and conditional logistic regression, the researchers estimated the relative odds of a pediatric asthma visit treated with prednisone associated with increased pollution concentrations in the previous 7 days. They re-ran these analyses separately for children receiving medications through the school-based intervention and children in a usual care control group.

The study found that interquartile increases in ultrafine particles and carbon monoxide concentrations in the previous 7 days were associated with increase in the relative odds of a pediatric asthma visit, with the largest increases observed for 4-day mean ultrafine particles and 7-day mean carbon monoxide. Relative odds estimates were larger among children receiving school-based inhaled corticosteroid treatment. The researchers observed no such associations with accumulation mode particles, black carbon, fine particles, or sulfur dioxide. Ozone concentrations were inversely associated with the relative odds of a pediatric asthma visit.

The researchers concluded that the findings suggest a response to markers of traffic pollution among urban asthmatic children. Effects were strongest among children receiving preventive medications through school suggesting that this group of children was particularly sensitive to environmental triggers. Medication adherence alone may be insufficient to protect the most vulnerable from environmental asthma triggers. However, more research is needed to confirm this finding.

This study was published in the journal *Environmental Research* in February 2014. More information on this is available at:

<http://www.sciencedirect.com/science/article/pii/S0013935113002028>.

New Study Finds Strong Association between Exposure to Fine PM and Cardiovascular Mortality – A new study in *Environmental Research* published in July 2014 demonstrates a strong association between exposure to fine particles emitted from fuel-burning engines and C-reactive protein (CRP), which is directly linked to deaths from cardiovascular disease.

The study conducted by scientists at the California Environmental Protection Agency’s Office of Environmental Health Hazard Assessment (OEHHA) is among the first to link long-term exposure to fine particle air pollution (PM_{2.5}) to elevated levels of CRP. High levels of CRP are key indicators of inflammation, which is the body’s response to inhaled irritating fine particles and is strongly associated with heart disease and stroke.

The study’s link between PM_{2.5} and CRP provides a plausible explanation for the previously documented connection between PM_{2.5} and cardiovascular mortality. The study, “Chronic PM_{2.5} exposure and inflammation: Determining sensitive subgroups in mid-life women,” found that:

- Diabetics and smokers experience particularly large effects of PM_{2.5} on CRP.
- People with low incomes, high blood pressure, or who are using hormone therapy may also be more vulnerable to PM_{2.5}.
- Statin medication and moderate alcohol consumption can reduce the impact of PM_{2.5} on CRP.

The study analyzed data from 3,000 women observed over a five-year period from the Study of Women’s Health Across the Nation cohort. Women recruited from six different metropolitan areas throughout the U.S. provided blood samples every year of the study. The researchers were able to isolate the effect of air pollution after taking into account other factors that might affect CRP.

More information on this study is available at:

<http://www.ncbi.nlm.nih.gov/pubmed/24792413>.

Effects of Concentrated Ambient Particles on Normal and Hypersecretory Airways in Rats – Epidemiological studies have reported that elevated levels of particulate air pollution in urban communities are associated with increases in attacks of asthma based on evidence from hospital admissions and emergency department visits. Principal pathologic features of chronic

airway diseases, like asthma, are airway inflammation and mucous hypersecretion with excessive amounts of luminal mucus and increased numbers of mucus-secreting cells in regions of the respiratory tract that normally have few or no mucous cells. The overall goal of the study was to understand the adverse effects of urban air fine particulate matter on normal airways and airways compromised with airway inflammation and excess mucus.

The project was specifically designed to: 1) examine the chemical and physical characteristics of PM_{2.5} and other airborne pollutants in the outdoor air of a local Detroit community with a high incidence of childhood asthma; 2) determine the effects of this community-based PM_{2.5} on the airway epithelium in normal rats compromised with pre-existing hypersecretory airway diseases; and 3) identify the chemical or physical components of PM_{2.5} that are responsible for PM_{2.5}-induced airway inflammation and epithelial alterations in these animal models. Two animal models of airway disease were used to examine the effects of PM_{2.5} exposure on pre-existing hypersecretory airways. A mobile air monitoring and exposure laboratory equipped with inhalation exposure chambers for animal toxicology studies, air pollution monitors, and particulate collection devices was used in this investigation. The mobile laboratory was parked in a community in southwestern Detroit during the summer months when particulate air pollution is usually high (July and September 2000).

The researchers monitored outdoor air pollution in this community daily, and exposed normal and compromised rats to concentrated PM_{2.5} from this local urban atmosphere. Rats in the inhalation studies were exposed for 1 day or for 4 or 5 consecutive days (10 hours/day) to either filtered air (controls) or concentrated ambient particles (CAPs) delivered by a Harvard ambient fine particle concentrator. Rats were killed 24 hours after the end of the exposure. Biochemical, morphometric, and molecular techniques were used to identify airway epithelial and inflammatory responses to CAPs. The Harvard concentrator effectively concentrated the fine ambient particles from this urban atmosphere (10-30 times) without significantly changing the major physicochemical features of the atmospheric particles. Daily CAPs mass concentrations during the 10-hour exposure period in July ranged from 16 to 895 $\mu\text{g}/\text{m}^3$ and in September ranged from 81 to 755 $\mu\text{g}/\text{m}^3$.

In general, chemical characteristics of ambient particles were conserved through the concentrator into the exposure chamber. Single or repeated exposures to CAPs did not cause adverse effects in the nasal or pulmonary airways of health rats. Variable airway responses to CAPs exposure were observed in rats with preexisting allergic airway disease induced by ovalbumin (OVA) sensitization and challenge. Only OVA-challenged rats exposed to CAPs for 5 consecutive days in September 2000 had significant increases in airway mucosubstances and pulmonary inflammation compared to saline-challenged/air-exposed control rats. OVA-challenged rats that were repeatedly exposed to CAPs in July 2000 had only minor CAP-related effects. In only the September 5-day exposure protocol, PM_{2.5} trace elements of anthropogenic origin were recovered from the lung tissues of CAPs-exposed rats. Recovery of these specific trace elements was greatest in rats with OVA-induced allergic airway disease.

Additional laboratory experiments using intratracheal instillations of ambient PM_{2.5} samples were performed to identify bioactive agents in the CAPs to which rats had been exposed in the inhalation exposure component. Because the most pronounced effects of CAPs inhalation

were found in rats with OVA-induced allergic airways exposed in September, researchers ambient PM_{2.5} samples that were collected on 2 days during the September CAPs inhalation exposures to use for instillation. The results from this instillation component did not suggest what fractions of the CAPs may have been responsible for enhancing OVA-induced airway mucosubstances and pulmonary inflammation observed in the inhalation exposure component. In summary, inhaled CAPs-related pulmonary alterations in the affected OVA-challenged rats appeared to be related to the chemical composition, rather than the mass concentration, to which the animals were exposed. Results of the trace element analysis in the lungs of CAPs-exposed rats exposed in September suggested that air particles derived from identified local combustion sources were preferentially retained in allergic airways. These results demonstrate that short-term exposures to CAPs from this southwestern Detroit community caused variable responses in laboratory rats and suggest that adverse biological responses to ambient PM_{2.5} may be associated more closely with local sources of particles and weather patterns than with particle mass.

This study was published by the Health Effects Institute in August 2004. More information on this is available at: <http://www.ncbi.nlm.nih.gov/pubmed/15543855>.

WHO Releases Report on Health Effects of PM – In July 2014, the World Health Organization (WHO) released a report on the health effects of PM. The report notes that one issue of concern is that monitoring of PM is very limited in the countries of eastern Europe, the Caucasus and central Asia. The paper summarizes the evidence about the health effects of air pollution from PM and presents the policy implications, the aim being to stimulate policy-makers to develop more effective strategies to reduce air pollution and its health effects in those countries.

A copy of the paper is available at:
http://www.euro.who.int/_data/assets/pdf_file/0006/189051/Health-effects-of-particulate-matter-final-Eng.pdf?ua=1.

ULTRAFINE PM

Researchers Publish Study on PM_{2.5} Constituents and Hospital Visits in Shanghai – This month, Chinese researchers published the results of a study that examined the short-term association between PM_{2.5} constituents and emergency room visits in Shanghai, China. The researchers measured daily concentrations of PM_{2.5}, organic carbon (OC), elemental carbon (EC), and eight water-soluble ions between January 1, 2011 and December 31, 2012. They analyzed the data using overdispersed generalized linear Poisson models. During the study period, the mean daily average concentration of PM_{2.5} in Shanghai was 55 µg/m³. Major contributors to PM_{2.5} mass included OC, EC, sulfate, nitrate, and ammonium. For a 1-day lag, an interquartile range increment in PM_{2.5} mass (36.47 µg/m³) corresponded to 0.57% increase of emergency room visits. In the three models used, the researchers found significant positive associations of emergency room visits with OC and EC. Their findings suggest that PM_{2.5} constituents from the combustion of fossil fuel may have an appreciable influence on health impact attributable to PM_{2.5}. More information on this is available at: pubs.acs.org/doi/abs/10.1021/es501305k?journalCode=esthag.

Epidemiological Evidence on Human Effects of Ultrafine Particles – Evidence from epidemiologic studies linking ambient concentrations of particulate matter to morbidity and mortality influenced the guidelines for air quality standards worldwide. With the improvement of measurement techniques, clearer effects were observed with smaller particle sizes. Based on these effects and results from animal studies on the potential toxicity of ultrafine particles, recent epidemiologic studies focus on the health effects of particles which are less than 100 nm in diameter. However, most of the studies are ongoing and only few results have been available so far. Six panel studies with patients suffering from chronic pulmonary diseases have been performed in Germany, Finland and the United Kingdom. Overall, a decrease of peak expiratory flow and an increase of daily symptoms and medication use was found for elevated daily particle concentrations. Effects were seen with both fine and ultrafine particles. One large study on daily mortality from Germany showed comparable effects of fine and ultrafine particles in all size classes considered. However, fine particles showed more immediate effects while ultrafine particles showed more delayed effects on mortality. The limited number of epidemiological studies suggest that there are health effects of fine and ultrafine particles which might be independent of each other. The study reviewed more than 30 references.

This study was published in the *Journal of Aerosol Medicine* in July 2004. More information on this is available at:
<http://online.liebertpub.com/doi/abs/10.1089/089426802320282310>.

HEI Releases New Report on Health Effects of Ultrafine Particles – On January 23, 2013, the Health Effects Institute (HEI) released a new report that concludes that, while there have been a growing number of laboratory and field studies of the effects of ultrafine particles (UFPs), “toxicologic studies in animals, controlled human exposure studies, and epidemiologic studies to date have not provided consistent findings on the effects of exposures to ambient levels of UFPs, particularly in human populations.” The report, “Understanding the Health Effects of Ambient Ultrafine Particles,” concludes that the “current evidence does not support a conclusion that exposures to UFPs alone can account in substantial ways for the adverse effects that have been associated with other ambient pollutants such as PM_{2.5}.” The expert panel formed by HEI reviewed over 300 studies, and the final report was peer reviewed by 10 outside experts.

According to Dan Greenbaum, president of HEI, “there is extensive evidence today that the complex mix of fine airborne particulate matter, PM_{2.5}, can contribute to a variety of cardiovascular respiratory and other health effects. But despite a large number of studies of the smallest particles (particles less than 0.1 microns in diameter), our expert panel found that the evidence to date has not confirmed the hypothesis of some in the scientific community that these ultrafine particles are the principle reason for these broader PM_{2.5} health effects.”

Particulate matter emissions are a complex mixture, containing particles of a variety of sizes and composition, and there have been continuing questions from the scientific and policy communities about whether some components or characteristics of that mixture, or particles from some sources, are more toxic and deserving of priority efforts for control. The ultrafine particles, which are emitted from a variety of sources, including traffic, industry, and cooking, have gained

special attention because of their potential for traveling deeper into the lungs, into the bloodstream, and into the brain. They are important as well because a number of regulatory actions in Europe and the U.S. have required new filters on diesel engines to reduce UFP emissions, while at the same time fuel economy rules are encouraging the use of more fuel-efficient gasoline engines that may increase UFP emissions.

A copy of the report is available at: pubs.healtheffects.org/view.php?id=394.

Study Identifies Toxicity of Fine and Ultrafine PM from Specific Sources – In May 2012, ARB and the Electric Power Research Institute (EPRI) released a report they commissioned by investigators at the University of California, Davis, that looks at how to distinguish health effects caused by different types of fine and ultrafine airborne particulate matter (PM) from different sources. This is among the first studies to examine the toxicology of particles according to their source of origin. Previous research has linked fine and ultrafine particles to asthma, heart disease, and other adverse health effects.

These particles, produced by emissions from many different sources, including traffic, industrial processes, wood-burning fireplaces, and gas- and coal-fired power plants, combine in the atmosphere and are affected by sunlight and other meteorological variables. National Ambient Air Quality Standards (NAAQS) do not distinguish between these sources since they are based solely on mass in a given particle size range. In addition, the mixing makes it difficult to determine which compounds in PM may be responsible for specific health effects.

The research was conducted by Dr. Anthony Wexler, director of the Air Quality Research Center at the University of California, Davis. Dr. Wexler used a single particle mass spectrometer and ten particle samplers to capture ambient particles. He then developed novel methods to extract PM from the filter and polyurethane foam substrates, so that as much as the PM was extracted from the substrates and hydroscopic and hydrophobic compounds in the PM were extracted evenly.

Laboratory mice were exposed to the separated particles, and their responses were monitored for signs of toxicity by Dr. Kent Pinkerton, a professor of pediatrics at the UC Davis School of Medicine. The analysis showed different levels of toxicity for different PM samples, associated with a variety of sources, such as traffic and wood smoke. Most of the toxicity was associated with automobile and cooking sources in both seasons, while in the winter toxicity was also associated with secondary compounds. Ultrafine particles were more potent inducers of inflammatory markers and cell death than larger particles.

Broadly, the study found that:

- Based on particle size, ultrafine PM was a more potent inducer of inflammatory and cytotoxic response compared to submicron fine PM on a per mass basis.
- For pulmonary inflammation and cytotoxicity, samples containing PM from vehicular sources or metals had the highest biological response for summer samples, while PM from vehicular sources, regional processes background, and nighttime inversions had the highest response for winter samples.

- In general, the same PM sample produced greater inflammatory and cytotoxic responses in lung samples than in the blood samples under the conditions used in this study.
- Analysis of systemic inflammation did not reveal major differences between the collected samples.

On February 19, 2013, Drs. Wexler and Pinkerton held a seminar to discuss this study at the Cal/EPA building in Sacramento. A copy of the final report is available at: www.arb.ca.gov/research/apr/past/06-331.pdf, and a copy of the presentation slides presented during the seminar is available at: www.arb.ca.gov/research/seminars/wexler5/wexler5.pdf.

Predicting Primary PM_{2.5} and PM_{0.1} Trace Composition for Epidemiological Studies in California – Epidemiological studies have identified positive correlations between exposure to ambient airborne PM and increased health risk. Recent studies have attempted to link these health effects to particle size and/or composition using exposure estimates based on the measured ambient PM₁₀ or PM_{2.5} concentrations from central site monitors, which are usually sparse in time, space, chemical composition, and source origin information. Important particle size distribution and chemical composition information is not routinely available, especially for the ultrafine particle size fraction (PM_{0.1}) that has been shown to have greater toxicity than larger particles. A more accurate estimate of exposure to detailed particle size fractions and chemical components would improve the power of future epidemiological studies.

A variety of statistical and mechanical modeling techniques have been proposed to improve the accuracy of exposure estimates to air pollution. Land Use Regression models have been developed to predict the spatial distribution of exposure to primary traffic PM on scales of hundreds of meters, but corresponding regression models for other important particle sources have not been widely demonstrated. Regression models also do not directly address the issues of data sparseness in time, particle size, and particle composition. Some land use regression models and dispersion models have been developed to predict the spatial distribution of exposure to primary traffic PM on scales of hundreds of meters, but corresponding regression models for other important particle sources have not been widely demonstrated.

The objective of this study is to develop the University of California – Davis_Primary (UCD_P) CTM to predict detailed particle size, composition, and source information over a 7-year period that can be used in subsequent epidemiological studies for PM_{0.1} and PM_{2.5}. California is chosen as the focus area for the study because it has a large population exposed to high PM concentrations, accurate PM emissions inventories, and comprehensive ambient measurements for model evaluation. The ability of UCD_P predictions for mass and chemical component concentrations in the PM_{0.1} and PM_{2.5} factions is evaluated against ambient measurements; a companion study will evaluate the model ability for PM source apportionment.

The predicted and measured daily PM_{2.5} EC concentrations exhibited seasonal variation at the seven available monitoring sites with lower values during the summer and higher values during the winter.

More information on this study, published in the journal *Environmental Science Technology* in April 2014, is available at: <http://pubs.acs.org/doi/abs/10.1021/es404809j>.

Researchers find Ultrafine Particles Have Independent Health Impacts from Larger Particles – Using a quasi-experimental opportunity offered by greatly restricted air pollution emissions during the 2008 Beijing Olympics compared to before and after the Olympics, a team of U.S. and Chinese researchers conducted a study to compare ultrafine particles (UFPs) and fine particles (PM_{2.5}) in their associations with biomarkers reflecting multiple pathophysiological pathways linking exposure and cardiorespiratory events. Number concentrations of particles (13.0–764.7 nm) and mass concentrations of PM_{2.5} were measured at two locations within 9 km from the residence and workplace of 125 participating Beijing residents. Each participant was measured 6 times for biomarkers of autonomic function (heart rate, systolic and diastolic blood pressures), hemostasis (von Willebrand factor, soluble CD40 ligand, and P-selectin), pulmonary inflammation and oxidative stress (exhaled nitric oxide and exhaled breath condensate pH, malondialdehyde, and nitrite), and systemic inflammation and oxidative stress (urinary malondialdehyde and 8-hydroxy-2'-deoxyguanosine, plasma fibrinogen, and white blood cells). Linear mixed models were used to estimate associations of biomarkers with UFPs and PM_{2.5} measured 1–7 days prior to biomarker measurements (lags).

The researchers found that the correlation coefficient for UFPs at two locations (~9 km apart) was 0.45, and at the same location, the correlation coefficient for PM_{2.5} vs UFPs was –0.18. Changes in biomarker levels associated with increases in UFPs and PM_{2.5} were comparable in magnitude. However, associations of certain biomarkers with UFPs had different lag patterns compared to those with PM_{2.5}, suggesting that the ultrafine size fraction (≤ 100 nm) and the fine size fraction (~100 nm to 2.5 μ m) of PM_{2.5} are likely to affect PM-induced pathophysiological pathways independently.

The findings suggest that number concentrations of UFPs monitored in a central site may be useful in a panel study design that mainly relies on within-person comparisons and when subjects work and resides within a relatively small area (<9 km radius). The results of this study suggest that particle emission controlling policies need to consider both the ultrafine and the fine size fraction of PM_{2.5} in order to protect human health.

The complete study results are published in *Environmental Science & Technology*, published in March 2014: <http://pubs.acs.org/doi/full/10.1021/es5006016>.

PM AND PREMATURE MORTALITY

SCAQMD Releases Latest Air Toxics Study, Concludes 57% Drop in Cancer Risk Since 2005 – The South Coast Air Quality Management District has released its Multiple Air Toxics Exposure Study IV (MATES IV) report, a monitoring and evaluation study conducted in the South Coast Air Basin. The study is a follow up to previous air toxics studies in the Basin and is part of the SCAQMD Governing Board Environmental Justice Initiative.

The MATES IV Study consists of several elements. These include a monitoring program, an updated emissions inventory of toxic air contaminants, and a modeling effort to characterize risk across the basin. The study focuses on the carcinogenic risk from exposure to air toxics. It does not estimate mortality or other health effects from particulate exposures.

The report concludes that the Southern California's air is getting healthier and with that the risk of developing cancer from inhaling toxins has fallen significantly. Compared to previous studies of air toxics in the Basin, this study found decreasing air toxics exposure, with the estimated Basin-wide population-weighted risk down by about 57% from the analysis done for the MATES III time period in 2005. Concerted efforts to reduce emissions from diesel trucks and other vehicles account for much of the drop. However, risks persist from toxic pollutants such as diesel PM and benzene. Air management district officials noted that calculations of cancer risk from the particles have been underestimated. The California Office of Environmental Health Hazard Assessment found that actual cancer risk due to the toxins tracked in the study is about three times greater than current state guidelines suggest. Those findings are being reviewed and the guidelines could be updated in 2015, which would increase the cancer risk figures the air district has reported over the years.

The area of greatest concern remains around the ports of Los Angeles and Long Beach where thousands of trucks and ocean-going vessels carry goods near neighborhoods. Air-associated cancer risk there is at least double that of other urban areas of Los Angeles, Orange, Riverside, and San Bernardino counties.

A copy of the MATES IV report is available at: www.aqmd.gov/docs/default-source/air-quality/air-toxic-studies/mates-iv/mates-iv-draft-report-10-1-14.pdf?sfvrsn=4. A SCAQMD press release announcing the report is available at: www.aqmd.gov/home/library/public-information/2014-news-archives/mates-iv-pr.

NASA Map Shows Deadliest Places on Earth Associated with PM2.5 Air Pollution –
A newly published map based on NASA-sponsored computer modeling of air quality shows the regions of the planet that suffer the highest annual premature death rates associated with levels of fine particulate air pollution (PM2.5). The global map was put together by Jason West, an earth scientist at the University of North Carolina, who is investigating the health impacts of air pollution. Based on models put together by West and his team, he estimates that 2.1 million premature deaths each year across the globe are the result of exposure to fine particulates that are emitted by motor vehicles, industrial smokestacks, and other sources. The highest levels of fine particulate emissions are found in East Asia, India, Indonesia, the Philippines, and some parts of Central Europe where mortality rates due to fine particulate pollution approach 1,000 premature deaths per square kilometer each year. Areas that are relatively “safe” from mortality associated with particulate emissions include the southeastern United States and interior regions of South America. Both of these regions have significantly reduced the levels of agricultural burning over the past 100 years. This graphic representation of global fine particulate air pollution, released in September 2013, is available at: www.theatlanticcities.com/technology/2013/09/heres-where-youre-most-likely-die-air-pollution/6946/. The scientific study on which the map is based is available here: iopscience.iop.org/1748-9326/8/3/034005/article.

New Study Finds Association Between Reductions in PM2.5 Levels and Improved Life Expectancy in U.S. – A new study led by researchers at the Harvard School of Public Health (HSPH) has found an association between reductions in fine particulate matter and improved life expectancy in 545 counties in the U.S. from 2000 to 2007. It is the largest study to date to find beneficial effects to public health of continuing to reduce air pollution levels in the U.S. Controlling for socioeconomic status, smoking prevalence, and demographic characteristics, the results showed that a decrease of 10 micrograms per cubic meter in the concentration of PM2.5 during the period from 2000 to 2007 was associated with an average increase in life expectancy of 0.35 years in 545 U.S. counties.

The study, which appears in the journal *Epidemiology* published in December 2012, looked at the effect on health of fine particulate matter (PM2.5). Numerous studies have shown associations between acute and chronic exposure to fine particle air pollution and cardiopulmonary disease and mortality. Studies have also shown that reductions in air pollution are associated with reductions in adverse health effects and improved life expectancy. Air pollution has been declining steadily in the U.S. since 1980, but the rate has slowed in the years since 2000. The HSPH researchers wanted to know whether the relatively smaller decreases in PM2.5 levels since 2000 are still improving life expectancy.

The research expanded on a 2009 study published in the *New England Journal of Medicine* by some of the same authors that found that reduced air pollution was associated with increased life expectancy in 211 urban counties. This new study looked at more recent data, more than two-and-a-half times as many counties, and included both rural and urban areas. The findings showed that there's a stronger association between declining air pollution and increased life expectancy in more urban, densely populated areas than in rural areas. The results also suggested that reduced levels of air pollution may be more beneficial to women than to men. As to why there was a stronger association between reductions in PM2.5 and improvements in life expectancy in urban areas, the researchers speculated that the composition of the particulates there may be different from that in rural areas.

More information on this is available at: www.eurekalert.org/pub_releases/2012-12/hsop-dap120312.php.

EPA Research Finds Exposure to Ozone and PM2.5 Can Lead to Premature Death – According to research completed last year by EPA scientists, exposure to ozone and fine particulate matter (PM2.5) can lead to premature death in populations that are not already gravely ill, which proponents say could help justify stricter ambient air standards for the two criteria pollutants. The research, published in the January 2012 edition of the journal *Risk Analysis*, finds that 130,000 to 340,000 premature deaths are attributable to exposure. The paper, “Estimating the National Public Health Burden Associated with Exposure to Ambient PM2.5 and Ozone,” indicates that “premature mortality attributable to poor air quality is not associated only with those already near death (sometimes called mortality displacement),” the Society for Risk Analysis said in a February 6, 2012 statement announcing the work. “These findings are in agreement with many other studies, showing that improved air quality has yielded a direct positive impact on life expectancy and does not affect only those individuals near the end of life.”

According to the paper, “among populations aged 65-99, we estimate nearly 1.1 million life-years lost from PM2.5 exposure and approximately 36,000 life-years lost from ozone exposure. These results show that despite significant improvement in air quality in recent decades, recent levels of PM2.5 and ozone still pose a nontrivial risk to public health.” The findings also show greater health effects in urban areas, including New York, Pittsburgh, and Houston, than elsewhere. EPA researchers note that their findings are based on 2005 data and that they do not take into account air quality improvements since then. One source says the research shows there is need for more work to be done in reducing PM2.5 and ozone levels, and it may boost EPA’s efforts to tighten the ambient air quality limits for these pollutants

The release of the study comes as EPA sent a February 3, 2012 letter to House Energy and Commerce Chairman Fred Upton (R-MI) noting that people are dying at PM2.5 levels below the current PM2.5 national ambient air quality standard. The letter is in response to December 14 questions Upton raised about the agency’s cost-benefit analysis of its air regulations. One environmentalist says EPA’s reply to Upton’s questions “make it crystal clear that the current national fine particle soot standard is far too weak. Indeed, EPA reports that people are dying from breathing particle soot levels that are ‘significantly below’ the arbitrary Bush standard...”

To view the study, go to: onlinelibrary.wiley.com/doi/10.1111/j.1539-6924.2011.01630.x/full.

Modeling Source-Attributable Health Impacts of Ambient Particulate Matter Exposure: Global Premature Mortality from Surface Transportation Emissions in 2005 – Outdoor exposure to ambient particulate matter was responsible for 3.2 million annual premature deaths in 2010 and is among the top ten leading risk factors for early death. While comprehensive air quality management is an effective strategy for air quality control in much of the developed world, the capacity to implement this approach in the developing world is generally weak. Nonetheless, developing countries have demonstrated an ability to enact sector-specific measures as a means of bottom-up air quality control. This study addresses the ongoing lack of information on sector-specific health impacts from ambient particulate matter exposure in order to inform new air quality improvement measures. The focus of this analysis is on the surface transportation sector.

This study introduces the Transportation Attributable Fraction (TAF), a relative value that expresses the fraction of ambient PM concentrations attributable to surface transportation at any point in space and time. In 2005 the researchers estimate the global population-weighted average TAF was 8.5%, representing an average exposure of 1.75 $\mu\text{g}/\text{m}^3$ per person. Approximately 247,000 annual premature deaths were attributable to surface transportation emissions, dominated by China, the U.S., the European Union and India. The global average crude mortality rate was 3.8 deaths per 100,000 and was highest in Western and Central Europe.

The researchers concluded that the surface transportation emissions were a significant global source of premature deaths in 2005. The study demonstrated how sector-specific health burden can be estimated using outputs from the Global Burden of Disease or other estimates of ambient PM health burden.

More information on this is available at:
<http://www.healtheffects.org/Pubs/AnnualConferenceBook2014.pdf>.

PM EFFECTS ON COGNITIVE AND NEUROLOGICAL FUNCTIONS

Study Warns on Possible Air Pollution Link to Neuroinflammatory, Alzheimer and Parkinson's Pathologies in Children – According to a study led by University of Montana Professor Lilian Calderon-Garciduenas and her colleagues, children living in polluted megacities are at increased risk for brain inflammation and neurodegenerative changes, including Alzheimer or Parkinson's disease.

Calderon-Garciduenas and her team compared 58 serum and cerebrospinal fluid samples from a control group living in a low-pollution city and matched them by age, gender, socioeconomic status, education levels achieved by their parents to 81 children living in Mexico City. The results found that the children living in Mexico City had significantly higher serum and cerebrospinal fluid levels of autoantibodies against key tight-junction and neural proteins, as well as combustion-related metals.

The breakdown of the blood-brain barrier and the presence of autoantibodies to important brain proteins will contribute to the neuroinflammation observed in urban children and raises the question of what role air pollution plays in a 400% increase in multiple sclerosis cases in Mexico City, making it one of the main diagnoses for neurology referrals.

Calderon-Garciduenas points out that there is a need for a longitudinal follow-up study to determine if there is a relationship between the cognition deficits and brain MRI alterations previously reported in Mexico City children, and their autoimmune responses. What is clear, however, is that the children are suffering from immune dysregulation. Once there is a breakdown in the blood-brain barrier, not only will particulate matter enter the body but it also opens the door to harmful neurotoxins, bacteria and viruses. The autoimmune responses are potentially contributing to the neuroinflammatory and Alzheimer's and Parkinson's pathology they are observing in young urban children.

While the study focused on children living in Mexico City, others living in cities where there are alarming levels of air pollution such as Los Angeles, Philadelphia-Wilmington, New York City, Salt Lake City, Chicago, Tokyo, Mumbai, New Delhi or Shanghai, among others, also face major health risks. In the U.S., 200 million people live in areas where pollutants such as ozone and fine PM exceed the standards.

More information on this is available at:
<http://iospress.metapress.com/content/xx6582688105j48h/?p=823f040ead0940a8a2bd15295c6a8ffe&pi=0>.

Study Links PM2.5 Exposure to Physical Changes in Brain – According to new research in mice, long-term exposure to air pollution can lead to physical changes in the brain, as well as learning and memory problems and even depression. Laura Fonken, lead author of the

study and a doctoral student in neuroscience at Ohio State University, stated that, while other studies have shown the damaging effects of polluted air on the heart and lungs, this is one of the first long-term studies to show the negative impact on the brain. For this study, Fonken and colleagues in Ohio State's Department of Neuroscience collaborated with researchers in the university's Davis Heart and Lung Research Institute. In previous studies in mice, the Davis research group found that fine air particulate matter causes widespread inflammation in the body, and can be linked to high blood pressure, diabetes, and obesity. This study, published in October 2011, aimed to extend their research on air pollution to the brain.

In the new study, mice were exposed to either filtered air or polluted air for six hours a day, five days a week, for 10 months. The polluted air contained fine particulate matter. The concentration of particulate matter that the mice were exposed to was equivalent to what people may be exposed to in some polluted urban areas. After 10 months of exposure to the polluted or filtered air, the researchers performed a variety of behavioral tests on the animals. The researchers also performed tests on the hippocampal area of the mice's brains. Results showed clear physical differences in the hippocampi of the mice who were exposed to polluted air compared to those who weren't. In addition, several of the co-authors of this study from the Davis research center found that chronic exposure to polluted air leads to widespread inflammation in the body, which is linked to a variety of health problems in humans, including depression. The study found evidence that this low-grade inflammation is evident in the hippocampus.

A copy of this study is available for purchase at:
www.nature.com/mp/journal/vaop/ncurrent/full/mp201176a.html.

Neurotoxicity of Traffic-related PM on Human Brain Structure – This epidemiologic study aimed to investigate whether late-life exposures to particulate air pollutant affect: the risk for mild cognitive impairment (MCI)/dementia; and MRI-measured brain volumes. Exposures to ambient PM are a novel environmental determinant of cognitive functions of elderly. Recent data from animal studies highlighted the neurotoxicity of PM exposures near roadways. However, very little is known about the putative adverse effects of traffic-related PM exposure on aging brains. Diesel exhaust, an important contributor of ambient PM exposure from traffic sources, has well-documented neurotoxic effects in animals. The study examined whether diesel PM exposure affects different brain regions involved in human cognition, focused on association brain and hippocampus.

The researchers selected an ongoing, well-characterized and geographically-diverse population of older women, the Women's Health Initiative Memory Study (WHIMS) cohort. Structural brain MRI scans were obtained in 2005-2006 (aged 71-89 years) to quantify the volumes of gray matter and normal-appearing white matter of 1,403 WHIMS participants. Annual diesel PM exposure was assigned to each residential census tract in a nationwide spatiotemporal mapping of yearly diesel PM estimates. The researchers had previously used a generalized additive model to conduct census tract-specific temporal interpolation of diesel PM estimate and complete the nationwide spatiotemporal mapping of annual diesel PM exposures in 1996-2005. This approach was informed by the results of 4-level hierarchical models/spatiotemporal analyses of diesel PM estimates given by the EPA National-Scale Air

Toxics Assessment Program, which employed motor vehicle emission simulators and air pollution dispersion models.

The study showed that older women with higher cumulative exposures to diesel PM, compared to those with lower exposures, had smaller volumes of gray matter volumes associated with higher cumulative exposures were found in all three associated cortices (frontal, parietal, and temporal). Over the interquartile range of cumulative exposure to diesel PM from on-road mobile sources ($0.32 \mu\text{g}/\text{m}^3$), the multivariate-adjusted difference in mean frontal gray matter volume was 3.08 cm^3 , adjusting for geographic region, demographic features, socioeconomic status, lifestyle, and clinical characteristics including cardiovascular disease risk factors. The researchers found no statistically significant difference in the hippocampal volume associated with diesel PM exposure.

The researchers concluded that findings from their cross-sectional analyses support the hypothesized neurotoxic effects of traffic-related PM on association cortices. The observed smaller gray matter volume associated with diesel PM exposure was consistent with the emerging data on synaptic neurotoxicity in animals with PM exposures near roadways.

More information on this is available at:

<http://www.healtheffects.org/Pubs/AnnualConferenceBook2014.pdf>.

Exposure to Vehicle Emissions Results in Altered Blood Brain Barrier Permeability and Expression of Matrix Metalloproteinases and Tight Junction Proteins in Mice – Traffic-generated air pollution-exposure is associated with adverse effects in the central nervous system (CNS) in both human exposures and animal models, including neuroinflammation and neurodegeneration. While alterations in the blood brain barrier (BBB) have been implicated as a potential mechanism of air pollution-induced CNS pathologies, pathways involved have not been explained.

Recent studies report a positive correlation between exposure to high levels of air pollution and increased hospital admissions/occurrence for cerebrovascular events such as stroke. Air pollution exposure has also been associated with other adverse effects on the CNS including neuroinflammation and neurodegeneration, which are associated with dementia-related disorders such as Alzheimer's disease and Parkinson's disease. With stroke being the third leading cause of death in the Western-world, as well as the leading cause of adult disability; and with the prevalence of neurological disorders such as AD and PD, which affect more than 4 million people in the U.S. and an estimated 27 million worldwide, it is critical to identify risk factors, including environmental, which may cause progression of these pathologies. While the pathways associated with air pollution-exposure induced effects on the CNS are not fully understood, recent studies suggest that pollutants, including those derived from vehicular emissions, may disrupt the integrity of the BBB. BBB disruption, and resulting alteration in permeability, has been implicated in the pathology of neurodegenerative disease, states of neuroinflammation, rev in, and/or hemorrhagic transformation during ischemic stroke.

The goal of this study, published in December 2013, was to determine whether inhalation exposure to mixed vehicle exhaust (MVE) mediates alterations in BBB permeability, activation

of matrix metalloproteinases (MMP)-2 and -9, and altered tight junction (TJ) protein expression. The data from this study indicate that inhalation exposure to traffic-generated air pollutants promotes increased MMP activity and degradation of TJ proteins in the cerebral vasculature, resulting in altered BBB permeability and expression of neuroinflammation markers.

More information on this is available at:

<http://www.particleandfibretoxicology.com/content/10/1/62>.

New Study Finds Air Pollution Linked to Cognitive Decline in Later Years –

According to a new study, particulate matter in vehicle exhaust and other sources of air pollution may hasten cognitive decline in older adults. Jennifer Ailshire who co-wrote the report is with the Center for Biodemography and Population Health and the Andrus Gerontology Center at the University of California in Los Angeles. She, along with Philippa Clarke of the Institute for Social Research at the University of Michigan, Ann Arbor, say that based on their results, improvements in air quality may be an important strategy for reducing age-related cognitive decline.

There has been some evidence that people living in more polluted areas have greater rates of cognitive decline, and the link is not explained by wealth and other social factors, the researchers point out in the *Journals of Gerontology: Series B*, published in June 2014. They gathered information from one wave of a large ongoing survey started in 1986, and focused their analysis on 780 participants who were 55 years of age or older at the time of the 2001/2002 survey.

Routine measurement of air pollution by census tract did not start until the late 1990s. Cognitive function was measured by math and memory tests and participants got a score based on the number of cognitive errors they made. Air pollution levels for each participant's neighborhood were calculated using fine particulate levels reported by the EPA's Air Quality System. Ailshire and Clarke found the average PM_{2.5} concentrations in the study's participants' environments were 13.8 µg/m³, which is above the EPA's air quality standard of 12 µg/m³. Then they compared the cognitive error scores to pollution levels and found that people living in high pollution areas, with 15 µg/m³ or more of PM_{2.5} had error scores 1.5 times those of the participants who lived in low pollution areas with no more than 5 µg/m³.

The authors note that poverty and other social factors as well as health problems can influence cognitive function. And poorer neighborhoods tend to be more polluted. But after the researchers adjusted for education, employment, gender, marital status and several other factors, the differences in cognitive error rates remained. Scientists believe that PM may affect cognitive function in older adults by its harmful effects on the cardiovascular system, which is connected to the brain through blood vessels, and possibly by directly acting on the brain itself.

More information on this is available at:

<http://psychogerontology.oxfordjournals.org/content/early/2014/06/05/geronb.gbu064.short?rs=1>.

Study Links PM Air Pollution to Autism, Schizophrenia – According to a new study published in the journal *Environmental Health Perspectives*, particulate matter in air pollution may irritate very young brains enough to cause problems.

When mice younger than 2 weeks old were exposed to very small particle pollutants, their brains showed damage that is consistent with brain changes in humans with autism and schizophrenia.

Research on mice doesn't always translate to humans. But Deborah Cory-Slechta, professor of environmental medicine at the University of Rochester Medical Center and lead researcher in the study, said the results could lead to regulations on even the smallest types of pollutant particles.

Schizophrenia is a mental illness that interferes with a person's ability to think clearly, manage emotions, make decisions and relate to others. Autism, and autism spectrum disorder, are terms for complex disorders in brain development. The disorders are present in varying degrees, and include difficulties in social situations, verbal and nonverbal communication, and repetitive behavior. The causes of both are a source of controversy and confusion.

The University of Rochester Medical Center research built on other studies that have shown a link between air pollution and autism in children. Cory-Slechta noted in 2013 study in *JAMA Psychiatry*, formerly *Archives of General Psychiatry*, that reported children who lived with high levels of traffic-related air pollution during their first year were three times as likely to develop autism. The medical center's research took a new direction in trying to show whether ultrafine particles would damage the brain, and if so, how. The National Institute of Environmental Health Sciences, part of the National Institute of Health, financed the three-year study.

Larger particles regulated by the EPA actually are less harmful because the nose and lungs keep them out of the bloodstream. But very fine particles, which aren't regulated, can slip through, travel through the lungs and be picked up in the bloodstream.

The researchers exposed mice for specific periods of time to levels of air pollution found during rush hour in cities such as Los Angeles, Boston, Atlanta, and New York City. One group of mice was examined 24 hours after its final exposure, another group 40 days later and a third group 270 days later. There was evidence of permanent inflammation and high level of neurotransmitter that is seen in humans with autism and schizophrenia. However, that doesn't mean a line exists between pollution and brain disorders.

More information on this is available at:
<http://www.urmc.rochester.edu/news/story/?id=4100>.

Associations between Traffic-Related Black Carbon Exposure and Attention in a Prospective Birth Cohort of Urban Children – Ambient air pollution may have neurotoxic effects in children. Data examining association between traffic-related air pollution and attention remain sparse.

Researchers examined the associations between black carbon (BC), a marker of traffic particles, and attention measures ascertained at 7-14 years of age among 174 children in a birth cohort based in the Boston, MA, area. The researchers estimated the BC levels using a validated spatial-temporal land-use regression model based on residence during children's lifetime. The children completed the Conner's Continuous Performance Test (CPT) measuring omission errors, commission errors, and hit reaction time (HRT), with lighter scores indicating increased errors or slower reaction time. Multivariable-adjusted linear regression analyses were used to examine associations between BC and each attention outcome.

The children in the study were primarily Hispanic (56%) and Caucasian (41%); 53% were boys. The researchers found a positive association between higher BC levels with increased commission errors and slower HRT, adjusting for child IQ, age, sex, blood lead level, maternal education, pre- and postnatal tobacco smoke exposure, and community-level social stress. Notably, the association was weaker, though still positive, for the highest BC quartile relative to the middle two quartiles. Sex-stratified analysis demonstrated statistically significant associations between BC and both commission errors and HRT in boys, but BC was not significantly associated with any of the CPT outcomes in girls.

In this population of urban children, the researchers found associations between BC exposure and higher commission errors and slower reaction time. These associations were overall more apparent in boys than girls.

More information on this study, published in the journal *Environmental Health Perspectives* in June 2013, is available at:
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3701996/>.

Convergence of Human, Animal, and *In Vitro* Studies on the Effects of Air Pollution on the Brain – In addition to increased morbidity and mortality caused by respiratory and cardiovascular diseases, air pollution may also negatively affect the brain and contribute to central nervous system diseases. A major constituent of ambient ultrafine PM is represented by traffic-related air pollution, mostly ascribed to diesel exhaust. Human epidemiological studies and controlled animal studies have shown that exposure to air pollution may lead to neurotoxicity. In addition to a variety of behavioral abnormalities, two prominent effects caused by air pollution are oxidative stress and neuroinflammation, which are seen in both humans and animals and are confirmed by *in vitro* studies. Human and animal studies suggest that air pollution (and diesel exhaust) may cause developmental neurotoxicity and may contribute to the etiology of neurodevelopmental disorders, including autistic spectrum disorders. In addition, air pollution exposure has been associated with increased expression of markers of neurodegenerative disease pathologies.

More information on this study, published in the journal *BioMed Research International* in 2014, is available at: <http://www.hindawi.com/journals/bmri/2014/736385/>.

PM EFFECTS ON HUMAN REPRODUCTION

New Study Concludes that Carbon Nanoparticles in PM_{2.5} Can Lead to Miscarriage – A research team at Lanzhou University has found that carbon nanoparticles can pass through the placental barrier, causing damage to an unborn baby and leading to miscarriage, according to China Science Daily. The research result has been published in Scientific Reports in March 2014.

Dr Qi Wei, main author of the report, said tests on pregnant laboratory rats have proved that carbon nanoparticles can cross the placental barrier and invade the fetus' body, causing estradiol secretion to increase, and hormone secretion and blood vessels to decrease, which will delay the fetus' development, and lead to stillbirth and miscarriage. Professor Wu Wangsuo, corresponding author of the report, said research results have proved that carbon nanoparticles cause damage to the fetus.

The research has directly verified that particulate pollutants, PM_{2.5} included, can cause harm to pregnant people, Wu said, and warned those exposed to severe particle contamination. The paper also suggested treatments for pregnancy-related disease caused by pollutants, Wu added.

A copy of the study is available at:
<http://www.nature.com/srep/2014/140312/srep04352/full/srep04352.html>.

Study Finds Air Pollution Exposure in Second Trimester May Increase Asthma Risk in Children – According to a new study presented at the 2014 American Thoracic Society International Conference in San Diego, children who are exposed *in utero* to high levels of PM air pollution during the second trimester of pregnancy may be at greater risk of developing asthma in early childhood. The study was published in May 2014.

Fetal lung growth and structural development occurs in stages, the researchers explained, thus timing of exposure may have differential effects on postnatal disease risk. They assessed the windows of susceptibility to particulate air pollution exposure during pregnancy on childhood asthma onset in a prospective urban birth cohort.

The study included 430 full-term (≥ 37 weeks gestation at birth) children followed to age 7 years and their mothers. Daily exposure to air pollution from sources including traffic, power plants, and other industrial sources consisting of fine particles in the prenatal period was estimated based on where these mothers lived. These fine particles have been linked to the greatest health risk and previous studies have suggested that effects on pregnant women can be transferred to the growing baby.

Children's physician-diagnosed asthma was ascertained by maternal reports up to age 7 years. The team examined associations between weekly averaged prenatal PM_{2.5} levels and children's asthma using distributed lag models. This modeling framework describes delayed effects between predictors and an outcome and estimates associations at each week while adjusting for exposures at other weeks, assuming that the associations vary smoothly over

time during gestation. Effect modification by gender and maternal pre-pregnancy obesity was also examined.

The researchers found that exposure to higher levels of fine particles in the second trimester was most strongly associated with increased asthma onset among the children, particularly for those born to non-obese mothers. The effect of maternal obesity, another known risk factor of childhood asthma onset, may be so strong that it was difficult to determine additional effects of air pollution among children born to obese mothers in this setting, the researchers noted.

Separately, a study in the *American Journal of Respiratory and Critical Care Medicine* reported that exposure to high levels of traffic-related air pollution is associated with changes in the right ventricle of the heart that may contribute to the known connection between air pollution exposure and heart disease.

The study involved 3,896 participants in the Multi-Ethnic Study of Atherosclerosis who were free of clinical cardiovascular disease and who underwent cardiac magnetic resonance imaging (MRI). Using estimated exposure to outdoor NO_x at the homes of participants over the year preceding MRI, the authors found that increased exposure to NO_x was associated with an approximately 1.0 g (5%) increase in right ventricular mass and a 4.1 mL (3%) increase in right ventricular end-diastolic volume.

More information on this is available at: http://www.eurekalert.org/pub_releases/2014-05/ats-ape051214.php.

Adverse Reproductive Health Outcomes and Exposures to Gaseous and Particle Matter Air Pollution in Pregnant Women – This study aimed to identify sources and components of air pollution mixtures that contribute most to the adverse reproductive outcomes and to determine the effect modification by socioeconomic factors, race, and body mass index.

California birth certificate data (2001-2008) were obtained with maternal address at delivery, geocoded at parcel level whenever possible. Primary PM concentrations were modeled for 2000-2006, by emission sources and size fractions (PM_{0.1}, PM_{2.5}, and PM₁₀). Secondary particles for 2000-2008 were also modeled, with less detail on source origin. Monthly ambient ozone, NO₂ and PM_{2.5} from EPA monitoring network (2000-2008) were interpolated using Bayesian Kriging.

The researchers studied the relationships between low birth weight (LBW) in term born babies and interpolated O₃, NO₂, and PM_{2.5}, modeled primary PM by source and composition and traffic density in Los Angeles County, using generalized additive models adjusting for potential confounders.

The researchers found that in Los Angeles, slightly increased (LBW) risk are associated with primary PM_{2.5} and PM_{0.1} mass, with several sources (especially gasoline, wood burning and commercial meat cooking) of primary PM, and with species of primary PM (elemental and organic carbon), K, Fe, Cr, Ni, Ti). Slightly increased LBW risks are also associated with measured total PM_{2.5}, NO₂ and local traffic indices, but not with O₃. Stronger associations are

observed in infants born to Hispanic women, and women with low socioeconomic status, chronic hypertension, diabetes and high BMI.

Preterm birth risk increased by 9-10% and 17% for interpolated NO₂ and O₃, and interpolated total PM_{2.5}, respectively, per inter-quartile range increase in entire pregnancy exposure in California women. Associations with modeled primary PM are weaker but statistically significant. For primary PM_{2.5}, the strongest associations by source are for onroad gasoline, followed by onroad diesel, offroad gasoline and commercial meat cooking. Overall, associations appear slightly higher for PM_{0.1} than for PM_{2.5}. For PM_{2.5} composition, the strongest positive associations with preterm birth risk are observed for nitrate, ammonium, and secondary organic aerosols, followed by elemental carbon, organic carbon and potassium, with metals showing weak and generally non-significant associations. For PM_{0.1}, 8-11% increased risk is observed per inter-quartile range exposure of Al, Ti, V, Si, and SOA. Associations are generally higher in lower socioeconomic status and African American populations.

The researcher found a modest influence of traffic and meat-cooking related pollution on term low birth weight, and a stronger influence on preterm birth. Both secondary pollutants and species in primary PM are strongly associated with preterm birth.

More information on this is available at:

http://www.healtheffects.org/Archive/AnnConf2011_Poster_pdfs/Wu.pdf.

PM FROM ALTERNATIVE FUELS

Study Reports that Biodiesel PM May Have Greater Adverse Health Effects Than Diesel – A recent publication in the ACS journal *Environmental Science & Technology*, published in September 2013, characterized PM generated from petroleum diesel and a blend of 20% soy-derived biodiesel (B20) using the same engine and operating conditions and conducted experiments in two human cell cultures, as well as female mice. They found that, although the PM mass from the B20 fuel was a factor of two lower than B0, the concentrations of inflammatory mediators in the in vitro cells and bronchoalveolar lavage fluid of mice were 20-30% higher in the B20-treated cells on an equivalent mass basis.

The work was published by researchers from the University of Vermont using a 1.9-liter VW light-duty engine operated over a 9-mode steady-state test cycle. Particle measurements were made using a scanning mobility particle sizer. The B0 particles exhibited a single mode distribution centered around 51 nm whereas the B20 PM had a mode at 32.2 nm and a larger 51 nm shoulder. The surface area of the B20 particles was about two times higher than the B0 particles. The B0 particles consisted of 54% non-polar compounds of n-alkanes, alkenes, and a mixture of 16 PAHs. The polar compounds in the B0 were primarily esters, ketones, and acids. In contrast, the B20 PM was made up of 68% polar compounds and the PAH content was reduced by a factor of two relative to the B0 particles. Furthermore, the content of benzo(a)pyrene, a Class 1 carcinogen (according to IARC), was two times higher in B0 compared to B20. Both the in vitro and in vivo inflammation response from cytokine/chemokine

data to an equal mass of PM resulted in a higher response to B20 PM, suggesting that biodiesel PM may be associated with more significant health outcomes.

The authors suggest that the mechanism for the greater inflammatory response and reactive oxygen species (ROS) in the mice and cells treated with B20 PM may be linked to the larger polar or soluble organic component in B20 exhaust. The smaller size and higher surface area of B20 PM may also be a contributor to the adverse health effects observed in this study.

The full reference for this publication is: Naomi K. Fukagawa, Muyao Li, Matthew E. Poynter, Brian C. Palmer, Erin Parker, John Kasumba, and Britt A. Holmén (2013), “Soy Biodiesel and Petrodiesel Emissions Differ in Size, Chemical Composition and Stimulation of Inflammatory Responses in Cells and Animals,” *Environmental Science & Technology*, doi: 10.1021/es403146c, pubs.acs.org/doi/abs/10.1021/es403146c.

Study Characterizes PM Toxicity from Diesel Passenger Cars Using DPF and Biodiesel Fuel – A European study published recently in the *Journal of Environmental Science and Technology* looked at the influence of PM control technology and fuel types on PM emissions and health effects. The overall conclusions showed that both the use of a DPF and the use of B50 fuel reduced the PM mass emissions from the diesel light-duty vehicles; however, the biodiesel fuel did not reduce the hazard of engine emissions while the DPF did on a per distance driven basis as indicated by reduced cytotoxicity, oxidative stress, and pro-inflammatory potential.

The PM emissions from two diesel passenger cars certified to Euro 4 emission standards were characterized over four test cycles made up of composites containing the Urban Driving Cycle, Extra Urban Driving Cycle, and Artemis Urban and Artemis Rural Road Cycles. The 2.2 L Honda Accord was equipped with a DOC and an underfloor deNO_x catalyst; the 2.0 L Peugeot 407 came with a DOC, an iron-based metal fuel additive, and an uncatalyzed DPF. The vehicles were fueled with petroleum diesel containing 10 ppm sulfur and a 50% blend of petroleum diesel and rapeseed-derived biodiesel. PM from a constant volume sampling (CVS) system was collected on filters using a high volume sampler. PM samples were extracted and a number of toxicity responses were measured, including: oxidative potential, cytotoxicity, and pro-inflammatory markers.

The following observations were made by the authors and further discussed in the paper:

- Use of B50 reduced PM mass by 50% and PM emission rates were reduced by 95% using a DPF, dropping emissions below the Euro 5 limit.
- Per unit mass, PM from B50 caused more cytotoxicity and greater release of pro-inflammatory markers than petroleum diesel and on an equal mass basis may be more harmful. This was reduced on a kilometer basis.
- PM from DPF-equipped vehicles contains higher fraction of semi-volatiles which contributes >70% of the oxidative activity. This resulted in a higher pro-inflammatory response and cytotoxicity per mass of post-DPF PM versus non-filtered PM. However, on a per kilometer basis, PM emissions from a DPF-equipped vehicle were less cytotoxic with lower oxidative potential.

The toxic potential of PM can differ depending on the method or metric used and the authors suggest that a harmonized test protocol be used to compare results from different studies to allow conclusions on the impact on human health risks to be analyzed.

The complete reference for this paper is: Gerlofs-Nijland, M.E. et al, “Cell Toxicity and Oxidative Potential of Engine Exhaust Particulates – Impact of Using Particulate Filter or Biodiesel Fuel Blend,” *Environ. Sci. Technol.*, DOI: 10.1021/es305330y, 4/18/13, www.unboundmedicine.com/medline/citation/23597117/Cell_toxicity_and_oxidative_potential_of_engine_exhaust_particles_impact_of_using_particulate_filter_or_biodiesel_fuel_blend.

Characterization of Particulate Matter Emissions from a Current Technology Natural Gas Engine – A team of researchers conducted experiments to characterize the particulate matter size distribution, number concentration, and chemical composition emitted from transit buses powered by a EPA 2010-compliant, stoichiometric heavy-duty natural gas engine equipped with a three-way catalyst (TWC).

Results of the particle-size distribution showed a predominant nucleation mode centered close to 10 nm. PM mass in the size range of 6.04 to 25.5 nm correlated strongly with mass of lubrication-oil-derived elemental species detected in the gravimetric PM sample. Results from oil analysis indicated an elemental composition that was similar to that detected in the PM samples. The source of elemental species in the oil sample can be attributed to additives and engine wear. Chemical speciation of PM showed that lubrication-oil-based additives and wear metals were a major fraction of the PM mass emitted from the buses. The results of the study indicate the possible existence of nanoparticles below 25 nm formed as a result of lubrication oil passage through the combustion chamber. Additionally, the result of oxidative stress analysis on the PM samples indicated strong correlations with both the PM mass calculated in the nanoparticle-size bin and the mass of elemental species that can be linked to lubrication oil as the source.

More information on this study, published in the journal *Environmental Science & Technology* in June 2014, is available at: <http://pubs.acs.org/doi/abs/10.1021/es5005973>.

U.S. EPA AND CALIFORNIA ARB FUNDED RESEARCH PROJECTS ON THE HEALTH EFFECTS OF PM

U.S. EPA Clean Air Research Centers Awarded Funding to Investigate Health Effects of Air Pollution – The U.S. EPA Clean Air Research Center has awarded funding to the following organizations to research the health effects of air pollution. A list of EPA funded research projects on air pollution effects on health is available at: <http://www.epa.gov/ncer/clarcs/>.

- **University of Washington Center for Clean Air Research (UW CCAR):** Project Amount: \$8,000,000; Project Period: December 1, 2010 through November 30, 2015. The UW CCAR is focused on the cardiovascular health effects of near-roadway

pollution, a complex mixture of particle, vapor and gas phase components that vary by vehicle emission source, road surface, extent of physical aging and the type and degree of atmospheric processing and photochemical reactions. This exposure scenario is not only known to be of considerable health importance, it also serves as a prototypical case for developing research approaches to dealing with multi-pollutant exposure-effect relationships. The researchers' aim is to integrate exposure, epidemiological, toxicological, clinical, and statistical sciences to study cardiovascular hazards of fresh and aged roadway emissions and significantly advance their understanding of the components and reaction products that cause these effects.

Researchers from four institutions are joining in a multi-disciplinary effort to study health effects of near-roadway pollution in line with current efforts to move from a single-pollutant to a multi-pollutant perspective. The Center consists of five highly-integrated research projects and two facility cores (including a Biostatistics Core) that together have the following six tasks: 1) to characterize real-world near-roadway pollutant concentrations, particle size distributions and chemical composition; 2) to simulate realistic contrasting near-roadway multi-pollutant exposure atmospheres for laboratory animal and human studies; 3) to identify cardiovascular and immunologic effects and the pathogenic mechanisms of near-roadway exposures using animal models; 4) to identify cardiovascular and immunologic effects of near-roadway exposures in human clinical studies; 5) to identify effects of long-term exposure to traffic-derived particle and gases on sub-clinical measures of cardiovascular disease and DNA methylation in a multi-ethnic population; and 6) to develop a statistical and methodological framework for studying health effects of multi-pollutant mixtures.

The Center program of research addresses at least three of the research questions posed in the Request for Application (RFA): 1) pollutant health effects in a multi-pollutant context; 2) biological mechanisms underlying health effects; and 3) exposure-response relationships. Identifying the most hazardous components of near-roadway exposures will allow more focused, coordinated and effective air pollution health policy based on sound science to reduce health impacts of this multi-pollutant exposure.

More information on this is available at:

http://cfpub.epa.gov/ncer_abstracts/index.cfm/fuseaction/display.abstractDetail/abstract/9282/report/0.

- ***Great Lakes Air Center for Integrative Environmental Research (GLACIER)***: Project Amount: \$7,999,875; Project Period: January 1, 2011 through December 31, 2015. GLACIER is a multi-disciplinary center with the objective to explore one of the most prevalent and important global health-environmental interfaces: the interrelationships between facets of the cardiometabolic syndrome (CMS) and air pollution. CMS is among the leading causes of death and threats to worldwide health. In tandem, exposure to air pollution, most notably fine particle matter remains highly prevalent and ranks among the leading causes of global mortality. Inter-relationships and health impacts of this growing confluence between these two epidemics are of tremendous importance to elucidate. The researchers' previous research has elucidated that PM_{2.5} exposure plays a critical, yet

under-appreciated, role in eliciting or exacerbating several key facets of the CMS, including elevating blood pressure, impairing vascular function, and even worsening metabolic insulin sensitivity and adiposity over a chronic duration. The researchers have also found that the location of exposure, multi-pollutant context, and constituents within PM_{2.5} affect the responses. The full extent and importance of inter-relationships between CMS and air pollution, individual susceptibility, specific pollution components, multi-pollutant atmospheres, PM_{2.5}-ozone coexposures, and underlying mechanisms of toxicity are all key issues remaining to be clarified. The researchers' center's overall hypothesis is that PM_{2.5} and ozone are: 1) capable of eliciting multiple important adverse cardiometabolic health effects that are dependent on; 2) the local multi-pollutant milieu; 3) an individual's pre-existing cardiovascular (CV) and metabolic condition; and 4) the interactive toxicity of PM_{2.5} and ozone coexposure.

In conjunction with core facilities, GLACIER consists of 3 controlled exposure projects that each addresses specific aspects of the CMS-air pollution interface. The projects are scientifically integrated and interactive which will foster synergistic insights and cohesive synthesis of conclusions. The Exposure Characterization Core (ECC) is an integral part of all three Projects of the Great Lakes Air Center for Integrative Environmental Research. In coordination with and support of the GLACIER Research Projects, the ECC will provide measurements of multi-pollutant exposures for both human subject (Project 1) and animal toxicology (Project 2 and 3) studies. The overall objectives of the ECC are to: 1) determine the mass, size, and chemical composition of pollutants for each exposure period; 2) determine the atmospheric emission sources responsible for the observed exposure concentrations; and 3) provide a detailed assessment of the differences in air pollution composition, sources, and chemistry between each of the exposure sites across each of the Projects. The objectives of the GLACIER BDMC are to provide guidance for the statistical design and analysis of studies and data management services that allow for the integration of the data into a single platform that facilitates timely analysis for GLACIER investigations and projects. Specific aims for this Core are: 1) to assist GLACIER investigators with statistical and data aspects of their research by providing expertise in the design, conduct and analysis of studies in Project 1-3; 2) to establish a database for each project on a secure computerized system; and 3) to implement a website to allow data import and export in a secured, controlled environment with a user-friendly interface.

Project 1 aims to clarify in humans the mechanisms of adverse CMS responses and the concentration-response relationships of acute exposures to differing PM_{2.5} mixtures.

Project 2 aims to determine the short-term CV, autonomic and airway toxicity in rats exposure to differing PM_{2.5} mixtures.

Project 3 expands on the main theme by determining the CMS toxicity of differing longer-term exposures in mice. Each project will also investigate the role of pre-existing susceptibility and the comparative effects of PM_{2.5} mixtures derived from 2-3 dissimilar multi-pollutant milieus of regional importance. Toxic effects of PM_{2.5}, ozone, each alone and in combination, will be evaluated at each location.

The researchers will address: 1) temporal-response relationships to pollutant exposure and the development of CMS; 2) CMS effects of ozone and fine particle mixtures from 3 differing locations and their interactive toxicity; 3) the role of obesity and pre-existing cardiometabolic abnormalities in individual susceptibility; 4) concentration-response relationships for particles and ozone; and 5) mechanisms whereby air pollutants elicit CV and metabolic health effects. Their results will provide critical insights into the health effects of PM2.5, ozone, and their co-exposures in a multi-pollutant context.

More information on this is available at:

http://cfpub.epa.gov/ncer_abstracts/index.cfm/fuseaction/display.abstractDetail/abstract/9281/report/0.

- ***Multi-Scale Assessment of Health Effects of Air Pollution Mixtures Using Novel Measurements and Models:*** Project Amount: \$7,999,779; Project Period: October 1, 2010 through September 30, 2015.

A multi-institutional, multi-disciplinary Center is proposed to address critical issues relating to the public health impacts of ambient air pollution. The overarching theme of the Center is a focus on characterizing ambient air pollution mixtures and elucidating their role in human health risk associated with air pollution. Novel measurements and modeling approaches will be applied in the context of a tiered multi-scale assessment of the health risks of mixtures characterized based on: 1) biological considerations (oxidants); 2) environmental management (sources); 3) evidence-based considerations (traffic emissions); 4) empirical assessment (data-based approach).

Four Research Projects will be supported by three Cores: an Administrative Core, an Air Quality Core and a Biostatistics Core. Project 1 will develop and deploy instrumentation to measure oxidants (including aerosol reactive oxygen species) and other species of interest to better understand their origins and atmospheric transformation and for use in characterizing mixtures for the three health studies. Project 2 will make direct use of these measurements to confirm associations with markers of oxidative stress in commuters. Project 3 and 4 will use a combination of measurements and modeled air quality estimates in large population studies, with Project 3 investigating questions regarding risks of in utero and early life exposures to air pollutant mixtures in two major new birth cohorts and Project 4 assessing underlying consistencies in morbidity associations across selected cities that have comprehensive daily air pollution characterization. The health projects include assessment of potentially sensitive and vulnerable subpopulations.

More information on this is available at:

http://cfpub.epa.gov/ncer_abstracts/index.cfm/fuseaction/display.abstractDetail/abstract/9280/report/0.

- ***Air Pollution Mixtures: Health Effects Across Life Stages:*** Project Amount: \$7,997,561; Project Period: January 1, 2011 through December 31, 2015. The main objectives of the proposed Center are: 1) to investigate the acute and chronic health effects across life stages of six exposure metrics (short- and long-term exposures

to individual pollutants, pollution sources and multi-pollutant mixtures) on: cognitive/neuropsychological function, cardiovascular/endothelial function, inflammation, birth weight/growth, and CVD-related hospitalization/mortality, and 2) to identify susceptibility and vulnerability factors that modify these effects.

Project 1 will investigate the toxicity of air pollutant mixtures in Boston, focusing on the identification of pollutant characteristics that are responsible for the most toxic effects, including: individual components, combinations of components (mixtures), formation processes, and source types. Exposures will be generated using a novel integration of the ambient particle concentrator and photochemical chamber technologies. Sprague-Dawley rats will be exposed and toxicity will be assessed by changes in: in vivo oxidant response, blood pressure, inflammation, and vascular reactivity. Project 2-5 will examine the health effects of the six exposure metrics on multiple integrated specific health outcomes. Project 2 will examine effects of these exposure metrics on cognitive and neuropsychological function; cardiovascular and endothelial function; inflammation; and oxidative stress among elderly individuals living in New England enrolled in the Normative Aging Study. Project 3 will investigate effects of the six metrics on cognitive impairment and interference, as well as vascular and endothelial function, among middle-aged and older adults living in New England enrolled in the Framingham Offspring and Third Generation Study. Project 4 will investigate effects of the metrics on somatic growth, blood pressure, cardiovascular fitness, and cognition, in the Viva ongoing prebirth study of over 1,300 children from Eastern Massachusetts. Project 5 will estimate mortality and hospitalization risks in hundreds of counties across the U.S. It will also study two cohorts in New England to: 1) estimate risks of adverse birth outcomes using approximately 700,000 live births; and 2) assess mortality and morbidity risks using 2.3 million Medicare enrollees. These projects (2-5) will study the modifying effect of measures of susceptibility and vulnerability and will link outcomes to the same pollution mixtures across all life stages.

More information on this is available at:

http://cfpub.epa.gov/ncer_abstracts/index.cfm/fuseaction/display.abstractDetail/abstract/9283/report/0.

ARB Funded Research Projects on the Health Effects of PM – ARB has funded the following research projects to study the effects of PM on human health. A complete list of ARB funded research projects are available at: <http://www.arb.ca.gov/research/research-results.php?category=Health%20Exposure>.

- **Co-Exposure to PM and O₃: Pulmonary C Fiber Platelet Activation in Decreased HRV:** Contractor: UC Davis; Principal Investigator: Fern Tablin; Project Status: Active. Fine particulate matter (PM_{2.5}) and ozone (O₃) appear to be responsible for the majority of serious health effects related to air pollution exposure, although little is known about how these pollutants cause adverse health effects, or whether or not they have interactive or synergistic effects on health endpoints. The objective of this study is to examine a hypothesized mechanistic pathway for the cardiovascular effects of ozone and PM_{2.5}, and to examine whether the effects of co-exposure to these pollutants are additive or

synergistic in laboratory animals. Normal and spontaneously hypertensive rats with implanted telemetry units that record the electrocardiogram and breathing pattern will be exposed for six hours to filtered air, and PM_{2.5} and O₃ alone and in combination. At the end of exposure, multiple endpoints related to platelet, vascular endothelial, heart rate variability, cardiac arrhythmia, and nervous system function will be evaluated to assess the contribution of each mechanistic pathway to the health effects observed. Analyses will compare responses to ozone alone and PM_{2.5} alone to responses to filtered air and the combined exposure (PM_{2.5} and O₃).

More information on this is available at: http://www.arb.ca.gov/research/single-project.php?row_id=65194.

- **Cardiovascular Effects of Multi-Pollutant Exposure: Mechanisms and Interactions:** Contractor: UC Irvine; Principal Investigator: Michael Kleinman; Project Status: Active. The objective of this study is to investigate the atherosclerotic potential of ambient PM_{2.5} from the Irvine, CA area. Both intact particles and particles denuded of the semi-volatile constituents of PM_{2.5} will be used with and without concurrent exposure to ozone in a mouse model of atherosclerosis. The principle goals are to elucidate the role of the semi-volatile components of PM_{2.5} and ozone in the progression of atherosclerosis, and the extent to which concomitant ozone exposure interacts with disease progression.

More information on this is available at: http://www.arb.ca.gov/research/single-project.php?row_id=65184.

- **Risk of Pediatric Asthma Morbidity from Multi-pollutant Exposures:** Contractor: UC Irvine; Principal Investigator: Ralph Delfino, Project Status: Active. One of ARB's goals is the protection of sensitive populations, such as children, from air pollution impacts. Many studies have shown a link between PM exposure and asthma morbidity outcomes in children. While these studies have contributed to ARB's understanding of the health impacts of particle exposure in children, several issues regarding the biologically active components of PM remain to be addressed. For example, there is limited information on the health effects of two important classes of particles in California, primary organic aerosols (POA) directly emitted from combustion sources; and secondary organic aerosol (SOA), which are largely photochemically-produced. These classes of organic aerosols have different spatial and temporal variability and they are minimally correlated with each other in southern California. The study aims to analyze the possible relationship between asthma morbidity using hospital data for 7,954 children with asthma, and both regional and local exposures to PM including POA and SOA. This will be studied using PM predictions generated by regional air quality models. PM will be estimated for three particle sizes, including ultrafine, PM_{2.5}, and PM₁₀ along with estimates of the contributions of specific sources of PM. Other air pollutants such as ozone, nitrogen oxides, and carbon monoxide will also be estimated. The study will evaluate whether temporal and spatial variations of PM_{2.5} sources and species affect the association between PM_{2.5} mass concentrations and emergency department visits and hospital admissions for asthma. It will also

evaluate the association between air pollution susceptibility, including asthma recurrence and socioeconomic status and demographic factors. The study will leverage the daily POA and SOA exposure data from the University of California, Davis/California Institute of Technology Source Oriented Chemical Transport Model. The study is expected to provide new information on the association of asthma morbidity with multiple local and regional air pollutants and general particle composition. Findings will be relevant to efforts by ARB to control PM_{2.5} by assessing the importance of sources and components that are related to health outcomes.

More information on this is available at: http://www.arb.ca.gov/research/single-project.php?row_id=65031.

- **Health Effects of Central Valley Particulate Matter:** Contractor: UC Davis; Principal Investigator: Anthony Wexler; Project Status: Active.
Epidemiological studies have demonstrated that respiratory and cardiovascular health effects are most associated with particulate matter levels one to three days prior to the advent of adverse health responses. However, the temporal patterns for development of pulmonary and cardiovascular responses appear to differ. Little is understood as to whether adverse changes in respiratory and cardiovascular endpoints represent independent effects that have different time courses for development, or whether they represent a continuum of effects that share common biological pathways and are inter-related. In addition, past studies have evaluated all endpoints at the same time post-exposure. Because of this, little is known about the time course for development of respiratory and cardiovascular effects. This project will involve a series of experiments in the Central Valley of California designed to investigate how time lags in exposure increase or diminish pulmonary and cardiovascular responses in a species of mouse model that has similar pulmonary and systemic responses to PM as are observed in humans. The hypothesis of this project is that local pulmonary inflammatory responses in the airways of the lung precedes, and then initiates vascular inflammation and subsequent platelet activation. Platelet activation is a key factor in formation of thrombi (clots) in the systemic circulation, leading to heart attacks and stroke, which are among the leading causes of premature death that have been associated with PM exposure. The results of this project will provide critical data on the biological mechanisms through which PM adversely impacts health, and will specifically address the key question of the lack of concordance between respiratory and cardiovascular endpoints. This study will provide important information that will help to explain the biological basis of epidemiological associations between adverse health outcomes and PM, and provide needed biological support for state and national ambient air quality standards for PM.

More information on this is available at: http://www.arb.ca.gov/research/single-project.php?row_id=64854.

- **Location Specific Systemic Health Effects of Ambient Particulate Matter:** Contractor: UC Davis; Principal Investigator: Dennis Wilson; Project Status: Completed.
Previous work by the contractor and others demonstrates induction of a systemic pro-inflammatory and pro-coagulant state in response to inhalation of environmental

particulate matter. This work demonstrated PM exposure activated platelets to an enhanced state of reactivity and suggested this could be a key factor in adverse cardiovascular events. This project evaluated pulmonary inflammation and systemic inflammatory and platelet responses to fine and ultrafine ambient PM collected from an urban (Sacramento) and rural (Davis) location. The objective of these experiments was to determine whether prior chelation of transition metals with deferoxamine mesylate (DFM) or binding of bacterial source endotoxin by polymyxin B reduce pulmonary and systemic responses to PM_{2.5}. The contractor hypothesized those inflammatory responses to a more transition metal rich urban source PM_{2.5} would be inhibited more by metal chelation while rural source PM_{2.5} would be more affected by endotoxin binding. Adult mice were given intratracheal instillation of collected PM_{2.5} and pulmonary pathology, systemic cytokine concentrations, and platelet activation were evaluated 24 hours later. To better assess contributions of aromatic hydrocarbons, oxidants or pro-inflammatory responses to biologically active material like endotoxin, the contractor used laser capture microscopy to probe specific anatomic locations in lung for gene responses associated with each of these components. The results support the following conclusions:

- Urban source PM_{2.5} were significantly more pro-inflammatory than an equivalent dose by mass of rural source PM_{2.5}.
- DFM pre-treatment of urban source PM_{2.5} did not decrease PM induced pulmonary inflammation.
- Treatment with DFM alone led to significant systemic platelet activation.
- Pulmonary inflammatory responses to both urban and rural source PM_{2.5} were inhibited by pre-incubation of PM_{2.5} with polymyxin B.
- In contrast to several prior animal experiments that demonstrated significant activation of circulating platelets after exposures to concentrated ambient particulates for two-weeks in the field, this study with a single exposure dose found no evidence of platelet activation in response to instilled PM_{2.5} at 24 hours after exposure.
- Urban source PM_{2.5} elicited transcription of genes associated with polycyclic aromatic hydrocarbon metabolism, reactive oxygen species response elements and inflammation in small airways, pulmonary arterioles and alveolar parenchyma.

A copy of the final report, published in January 2014, is available at:

<http://www.arb.ca.gov/research/apr/past/10-302.pdf>.

- **Cardiopulmonary Health Effects: Toxicity of Semi-Volatile and Non-Volatile Components of Ultrafine PM:**

Contractor: UC Irvine; Principal Investigator: Michael Kleinman; Project Status: Completed.

The goal of the project was to determine whether or not the toxicity of ultrafine (UFP) particle depends on the concentration and composition of semi-volatile and non-volatile fractions of the PM. The researchers tested the hypothesis that adverse effects of exposure to these UFP, which are primarily emitted by combustion sources and are highly enriched in semi-volatile components, will be significantly attenuated by removal of those components from the aerosol. The researchers used a unique mobile in vivo rodent exposure system in combination with a particle concentrator and thermal denuder to study the cardiopulmonary effects of UFP, before and after the removal of the semi-

volatile components. The study used genetically modified mice that had impaired lipid metabolism and were therefore predisposed to the development of atherosclerotic-like plaques. Exposures were 6 hours/day, 4 days per week for 8 weeks and were conducted near the University of Southern California campus in central Los Angeles. Detailed chemical and physical characterization examinations of the concentrated ambient UFP (CAP) and thermally denuded CAPs were conducted. The thermal denuder removed more than 60% of the particle-associated organic compounds (OC) but did not remove the non-volatile components such as elemental carbon (EC) or trace metals. Exposure to undenuded CAPs accelerated the development of atherosclerotic plaque in the genetically modified mice, characterized by decreased arterial lumen diameters and increased incorporation of lipids in arterial walls. The lumen diameters and arterial wall lipid contents in the genetically modified mice exposed to thermally denuded CAPs suggested significantly less plaque development than in the mice exposed to undenuded CAPs and were not different from plaque levels in genetically modified mice exposed to purified air, as controls. In addition, heart rate variability was decreased in the mice exposed to undenuded CAPs but not in the mice exposed to either purified air or denuded CAPs.

In a separate experiment genetically modified mice were exposed to air, denuded CAPs and the particle free organic compounds (PFO) that were stripped from the CAPs in the thermodenuder and delivered to the exposure system. This study demonstrated that the organic compound, independent of the presence of particles, played an active role in the acceleration of plaque development. Cholesterol and low density lipoprotein-cholesterol (LDL) levels were relatively high in the genetically modified mice, as would be expected. Exposure to undenuded CAPs, denuded CAPs and PFO all induced increased levels of both cholesterol and LDL in the serum of these mice, but only the undenuded CAPs and the PFO cause significant serum lipid peroxidation, which is a known contributor to plaque formation. The researchers concluded that the organic constituents of UFP contribute to the accelerated development of atherosclerotic plaque in arteries, lipid oxidation is an important mechanism of action in PM-induced coronary artery disease, and that removal of the organic compounds from PM greatly ameliorates plaque development associated with air pollution exposure. These findings suggest the emission control measures that remove and sequester or destroy organic constituents of combustion generated aerosols could benefit public health because coronary artery disease is a leading contributor to heart-related deaths, which represents about 50% of deaths, annually, in California and other states as well.

A copy of the final report, published in April 2013, is available at:
<http://www.arb.ca.gov/research/apr/past/07-307.pdf>.

- **Toxicity of Source-Oriented Ambient Submicron Particulate Matter:** Contractor: UC Davis; Principal Investigator: Anthony Wexler; Project Status: Completed. Current National Ambient Air Quality Standards for particulate matter regulate the mass concentration of particles in the atmosphere. There is growing evidence that different sources of these particles have different levels of toxicity. In this work, a system was developed for collecting source oriented particles from the atmosphere suitable for toxicity testing. Briefly a single particle mass spectrometer identified particle sources in

real time; the mass spectrometer selected a ChemVol associated with each source category to collect size-selected PM while those particles were being observed. This system was operated in Fresno, CA during the summer of 2008 and winter of 2009. The toxicity of the collected samples was assessed in a mouse model. Samples were chemically analyzed to associate them with sources prevalent in Fresno, CA. Most of the toxicity was associated with automobile and cooking sources in both seasons while in the winter toxicity was also associated with secondary compounds.

A copy of the final report, published in May 2012, is available at:
<http://www.arb.ca.gov/research/apr/past/06-331.pdf>.

- **Systemic Platelet Activation in Mice Exposed to Fine Particulate Matter:** Contractor: UC Davis; Principal Investigator: Fern Tablin; Project Status: Completed. The contractor conducted five separate experiments designed to define the effects of ambient particles on the cardiovascular system. Mice were exposed to concentrated ambient particles (CAPs) less than 2.5 microns in diameter or instilled with PM_{2.5} from the Fresno, California area. Control animals were exposed to filtered air or physiological saline. Studies were conducted during summer and winter in both urban and rural areas. The three CAPS experiments were conducted in winter 2008, summer 2008, and evaluated the effects of CAPs on the vascular and hemostatic systems. Later studies examined the effects of short-term in vivo instillation of PM_{2.5} that was collected during the CAPS experiments. In all studies, it was determined the production of systemic inflammatory cytokines to evaluate the extent of pulmonary, coronary and systemic inflammation. Platelet upregulation and activation in response to agonist was evaluated by flow cytometry. They determined the expression and activation of key platelet integrins and the extent of alpha granule and lysosomal granule secretion. Complete blood counts were performed. Lung tissue was evaluated for change in gene expression either by gene array or by laser capture micro-dissection. Particle exposed animals showed platelet activation in all studies compared to control animals, while proinflammatory cytokines were predominantly upregulated in the winter CAPs and winter instilled exposures. Exposure to winter PM appears to activate different physiological outcomes than summer exposures.

A copy of the final report, published in February 2011, is available at:
<http://www.arb.ca.gov/research/apr/past/07-337.pdf>.

- **Extended Analyses of Air Pollution and Cardiovascular Disease in the California Teachers Study Cohort:** Contractor: Department of Health Services; Principal Investigator: Michael Lipsett; Project Status: Completed. Several studies have reported associations between long-term exposure to air pollution and mortality. A number of important questions remain, however, regarding the impact of how long-term exposure is measured, the existence of critical windows of exposure, the relative importance of various constituents of PM, the relationship of chronic exposure to new cases of disease, and the shape of the concentration-response function linking fine particulate matter with mortality. As an extension of previous work, researchers developed estimates of long-term air pollution exposure at the residences of

over 100,000 female participants in the longitudinal California Teachers Study (CTS). The researchers examined associations between several exposure metrics and the following outcomes: all-cause mortality, cause-specific mortality (principally diseases of the cardiovascular and respiratory systems), as well as new causes of both fatal and non-fatal heart attacks and stroke. To derive the pollutant exposure metrics, the researchers linked the CTS participants' addresses with monthly estimates of long-term exposure to PM_{2.5}, PM₁₀, ozone, carbon monoxide, nitrogen dioxide, nitrogen oxides, and sulfur dioxide. The main analyses examined potential relationships of mortality and disease incidence with long-term residential exposures to PM₁₀, ozone, CO, NO₂, NO_x, and SO₂ from 1996 through 2005, and to PM_{2.5} beginning in 1999, when the latter pollutant began to be systematically measured statewide. Participants' addresses were linked as well with several cross-sectional measures of potential traffic-related exposures from the year 2000. The researchers analyzed these relationships while adjusting for many individual –level and neighborhood variables, and undertook a variety of sensitivity analyses.

The researchers found elevated risks between long-term exposure to PM_{2.5} and mortality from ischemic heart disease as well as incidence of stroke, particularly among women who were post-menopausal at baseline. Long-term exposures to PM₁₀, ozone and NO_x were associated with elevated risks of ischemic heart disease mortality. PM₁₀ exposure was also linked incident stroke. The association of ozone with mortality was most likely due to its strong correlations with PM₁₀ and PM_{2.5}. Among never-smokers, NO_x exposure was associated with elevated risks of cardiovascular and ischemic heart disease mortality. The researchers did not find that women who had diabetes or who were overweight or obese were at increased risk of PM_{2.5}-associated effects. Traffic density, a measure of the estimated number of vehicle miles traveled within 150 meter of a participant's residence, was associated with all-cause, cardiopulmonary and cardiovascular mortality. In additional analyses of associations between long-term exposure to PM_{2.5} and mortality, the researchers found that: 1) the exposure-response relationship was best described as linear; and 2) significant effect estimates were evident by one year of exposure, with the magnitude of the association leveling off with increasing duration. This study provides additional evidence that long-term exposure to air pollution is associated with mortality from heart disease and demonstrates as well that exposure to PM is associated with the incidence of new cases of stroke.

A copy of the final report, published in October 2011, is available at:
<http://www.arb.ca.gov/research/apr/past/06-336.pdf>.

- **Spatiotemporal Analysis of Air Pollution and Mortality in California Based on the American Cancer Society Cohort:** Contractor: University of California, Berkeley; Principal Investigator: Jerrett Michael; Project Status: Completed. Studies using the American Cancer Society (ACS) Cancer Prevention II (CPS II) cohort to assess the relation between particulate air pollution and mortality rank among the most influential and widely cited. The original study, a reanalysis that introduced new random effects methods and spatial analytic techniques, and recent studies with longer follow-up and improved exposure assignment, have all demonstrated statistically significant and

substantively large air pollution effects on all-cause and cause-specific mortality. Due to this robust association and a lack of other large cohort studies on the long-term effects, the ACS studies have proven important to government regulatory interventions and health burden assessments.

Currently, there are no ACS CPS II statewide studies in California that investigate whether the risks are similar to or different from those reported in the ACS CPS II analyses. Existing estimates come from either national-level ACS studies, in which the California subjects comprise less than 15% of the total national sample, or from select metropolitan or county areas of California, where questions remain about their generalizability to the rest of the state. A need exists to investigate whether the results hold across California. Additionally, none of the existing ACS studies have used high-resolution exposure assignment or investigated the temporal dimensions of the dose-response relationship. In this study, the researchers used advanced exposure modeling to reduce problems of measurement error, and they investigated time windows of exposure.

The researchers identified more than 76,000 California subjects in the ACS cohort to serve as the study population (20,432 deaths with an 18 year follow-up ending in 2000). These subjects were widely distributed across California, giving comprehensive coverage for much of the population of the state. For the first time in using the ACS CPS II data, the researchers have geocoded subjects to their home address to refine their exposure assignment. The researchers assessed the association between air pollution and several causes of death, including cardiovascular (CVD), ischemic heart disease (IHD), respiratory, lung cancer, and other causes. The researchers also evaluated all-cause mortality. The researchers assessed the association between air pollution and death using standard and multilevel Cox proportional hazards models. Control was also applied for residence in the five largest urban conurbations, which potentially have different mortality rates than non-metropolitan areas.

The researchers concluded that taken together, the results from this investigation indicate consistent and robust effects of PM_{2.5}, and other pollutants commonly found in the combustion-source mixture with PM_{2.5}, on deaths from CVD and IHD. The researchers also found significant association between PM_{2.5} and all causes of death, although these findings were sensitive to model specification. In Los Angeles, where the monitoring network is capable of detecting intraurban variations in PM_{2.5}, the researchers observed large effects on death from all causes, CVD, IHD, and respiratory disease. These results were consistent with past ACS analyses and with findings from other national or international studies reviewed in this report. The strongest results were from a land use regression estimate of NO₂, which is generally thought to represent traffic sources, where significantly elevated effects were found on deaths from all causes, CVD, IHD, and lung cancer. The researchers therefore conclude that combustion-source air pollution is significantly associated with premature death in this large cohort of Californians.

A copy of the final report, published in November 2011, is available at:
<http://www.arb.ca.gov/research/apr/past/06-332.pdf>.

- **Effects of Inhaled Fine Particles on Lung Growth and Lung Disease:** Contractor: UC, Irvine; Principal Investigator: Michael Kleinman; Project Status: Completed. The Children's Health Study (CHS), conducted by the University of Southern California, has reported significant associations between reduced lung function growth and exposures to NO₂, acid vapor, PM_{2.5}, and elemental carbon. The primary objective of this study was to use an animal model to test the hypothesis that chronic PM_{2.5} exposure during the period of rapid lung growth and development can lead to reduced growth in pulmonary function that is related to oxidative stress and tissue injury. The researchers studied changes in the development of the mouse lung and lung function during chronic exposure to concentrated ambient PM_{2.5} using a mouse model. The mice were exposed from 3 weeks to 11 weeks of age. The study also evaluated whether observed deficits in lung function persisted for up to two weeks after exposure was terminated. Mice that were exposed to concentrated ambient fine particles (CAPs) for eight weeks had reduced pulmonary function, measured as increased respiratory resistance, that persisted for up to 2 weeks after the termination of exposure. The researchers preserved tissue, blood and bronchoalveolar lavage fluid samples for later analyses to investigate the relationship between pulmonary function deficits and alterations in lung structure, biochemical mediators of oxidative stress and inflammation, as well as alteration in gene expression that might be associated with lung development. The researchers also examined the associations between particle chemical composition, particle physical characteristics and particle concentrations and observed changes in pulmonary function. There were two sets of exposures: the first exposures were performed at "high" concentration (PM_{2.5}, 243 µg/m³; number concentration, 93,000 particles/cc) and the second exposures were at "low" concentration (PM_{2.5}, 56 µg/m³; particle number 83,000 particles/cc). Both studies produced significant increases in resistance. Particle mass concentrations in the low study were nearly 1/5th that in the high study, however the particle number concentrations were nearly the same, suggesting that high concentrations of ultrafine particles were present during both sets of exposures. There were methodological differences between the two sets of exposures, however the results suggest that the ultrafine components of PM_{2.5} may be more strongly associated with the observed decreases in resistance in the PM-exposed developing lung than are larger-sized particle components.

A copy of the final report, published in June 2010, is available at:

<http://www.arb.ca.gov/research/apr/past/05-342.pdf>.

- **Cardiovascular Health Effects of Fine and Ultrafine Particles During Freeway Travel:** Contractor: UC Los Angeles; Principal Investigator: William Hinds; Project Status: Completed. A 24-month study of human response to two-hour exposures to freeway air in Southern California was conducted. A nine-passenger van was modified with a high-efficiency filtration system that delivered filtered or unfiltered air to an exposure chamber inside the van. State-of-the-art instruments were used to measure concentration and size distribution of fine and ultrafine particles and the concentration of other pollutants associated with motor vehicles. Nineteen volunteer subjects (average age 71 years) rode for two hours each in filtered and unfiltered air on two freeways, I-405 and I-710.

Double-blind health assessments included 24-hour ambulatory ECG, blood biochemistry, blood pressure, and lung function. Mean unfiltered particle number concentration was 107,500 particles/cm³ for I-710 and 77,800 particles/cm³ for I-405; mean PM_{2.5} mass was 51.4 and 44.5 µg/m³, respectively. Filtration reduced particle count greater than 95% but did not remove gases. Atrial ectopic beat incidence during and after exposure decreased 20% on average with filtered air compared to unfiltered air. Individual responses related most strongly to particle count. Blood markers NT pro-BNP and VEGF decreased 30% on average in filtered air compared to unfiltered air.

A copy of the final report, published in January 2010, is available at:
<http://www.arb.ca.gov/research/apr/past/04-324.pdf>.

- **Ultrafine Particulate Matter and Cardiorespiratory Health:** Contractor: UC Irvine; Principal Investigator: Ralph Delfino; Project Status: Completed.
This is the first study conducted in California among vulnerable individuals with coronary artery disease on the acute cardiovascular health effects of exposures near subject residences to size-fractionated particles and to particle characteristics linked to mobile sources. The researchers conducted a comprehensive PM monitoring effort for a repeated-measures panel study aimed at evaluating acute cardiovascular health effects of exposure to PM. They followed 64 nonsmoking elderly individuals with coronary artery disease living in retirement communities in the Los Angeles Air Basin in California. Subjects were followed with 12 weekly blood draws for biomarkers and over 10 days with ambulatory electrocardiographs and blood pressure monitors. This project supplements the exposure assessment for an NIH-funded study. The researchers found the contribution of mobile sources to indoor PM levels was similar to their corresponding outdoor estimates. Analysis of the relation between PM redox activity and blood biomarkers was largely nonsignificant. However, analysis of health outcomes and direct air measurements revealed that primary combustion markers [elemental-black carbon, primary organic carbon, CO, NO_x-NO₂] were positively associated with blood pressure, electrocardiographic ST segment depression (an indicator of cardiac ischemia), biomarkers of systemic inflammation, and platelet activation, and were inversely associated with erythrocyte antioxidant enzymes. Particle number and particle < 0.25 µm were more strongly associated with biomarkers than particles 0.25-2.5 µm. Biomarker associations were stronger for indoor exposures to EC and PN of outdoor origin than uncharacterized indoor exposures. Overall results suggest that current regulations of particle mass may not completely represent particle size fractions and components important to protect public health of vulnerable populations. This likely includes particles < 0.25 µm and pollutant components linked to fresh traffic emissions, including indoor infiltrated particles from mobile sources.

A copy of the final report, published in April 2009, is available at:
<http://www.arb.ca.gov/research/apr/past/03-329.pdf>.

- **Air Pollution and Cardiovascular Disease in the California Teachers Study Cohort:** Contractor: California Department of Public Health; Principal Investigator: Michael Lipsett; Project Status: Completed.

There are few studies examining association between long-term exposure to air pollution and adverse health outcomes. In an ongoing cohort study of over 100,000 female participants in the California Teachers Study (CTS), the researchers developed estimates of long-term air pollution exposures at the subjects' residences and examined associations between these exposure estimates and the following health outcomes: total mortality, cardiopulmonary mortality, and incidence of both fatal and non-fatal heart attacks and stroke. In addition, they examined the potential impacts of several traffic metrics on these outcomes. In order to derive the pollutant to multiple air pollutants, including PM_{2.5}, PM₁₀, and several gases (including ozone, CO, NO₂), and traffic related exposures from the year 2000 or later. They analyzed these relationships while adjusting for many individual level and neighborhood variables, and undertook a variety of sensitivity analyses. The researchers found strong and consistent associations of PM_{2.5} not only with total and cardiopulmonary mortality, but also with incidence of heart attacks and stroke. They also identified somewhat less consistent relationships between one or more of these adverse outcomes and PM₁₀, CO, NO₂ and ozone. Most of the traffic metrics were not associated with these outcomes. This study provides additional evidence that long-term exposure to air pollutant is associated with mortality, and demonstrates as well that exposure to several combustion related pollutants is associated with the incidence of new cases of heart attacks and stroke.

A copy of the final report, published in October 2007, is available at:
<http://www.arb.ca.gov/research/apr/past/03-313.pdf>.

- **Particulate Air Pollution and Morbidity in the California Central Valley: A High Particulate Pollution Region:** Contractor: Kaiser Permanente, Northern California Region; Principal Investigator: Stephen Van Den Eeden; Project Status: Completed. The goal of this study was to evaluate the relationship between particulate air pollution and morbidity among the Kaiser Permanente (KP) membership who reside in the Central Valley (CV) of California. Daily augmented PM monitoring in the Central Valley was instituted as the November 1996 as part of a special monitoring program by the ARB. The combination of the ambient air pollution data collected as part of the enhanced monitoring and the morbidity data from Kaiser Permanente provided an excellent opportunity to explore this relationship in an area with varied PM.

The researchers conducted time-series analyses examining the association between daily ambient measures of PM (including PM chemical components), other criteria air pollutants (e.g., ozone, NO₂, and CO) and daily admissions to the emergency room or hospitalization for respiratory and cardiovascular conditions among members of Kaiser Permanente, Northern California Region (KPNC) living in the Central Valley of California. Only those KPNC members who resided in an area where exposure could be assigned using one or more of the PM monitoring stations were included in the study. The study period was from January 1996 to December 2000.

Exposure was assigned based on each KP member's residential zip code and linked to the city where a monitoring station was in place. Morbidity data were derived from computerized data sources at Kaiser Permanente. Each health event of interest was

identified and the age, gender and diagnosis ascertained. Outcome events were classified into one of three categories: cardiovascular, acute and chronic respiratory conditions, and two types of admissions; hospitalizations and emergency room visits. Preliminary analyses of the data included graphical techniques and bivariate analyses. Non-parametric smooths were developed that first fit confounding variables to each set of outcome data. These factors included long-wave terms (time), day-of-week, temperature, and humidity. In addition, because there were four population centers in this study a set of indicator variables for center was also included.

Consistent adverse health effects were observed between a variety of air pollution metrics and acute and chronic respiratory hospitalizations and emergency room visits among Kaiser Permanente members living in the Central Valley of California. These associations were consistent across type of analysis and type of admission. Of the pollutant studied PM10 and PM2.5 were consistently associated with increases in hospitalizations and emergency room visits for acute and chronic respiratory conditions. To a lesser extent CO and NO₂ were associated with increases in admissions for all outcomes in their study. In contrast to the PM10 and PM2.5 results, the researchers did not find convincing evidence of an association between the coarse fraction of PM and their outcomes. In addition, their results for cardiovascular admissions were inconsistently or not at all associated with the pollutants studied. Some of their pollutant-outcome associations were in the opposite direction from what they expected, most notably ozone.

A copy of the final report, published in July 2002, is available at:
<http://www.arb.ca.gov/research/apr/past/97-303.pdf>.

- **A Critical Review of the Particulate Matter Toxicology Literature For Senate Bill 25 Review of the Particulate Matter Standard:** Contractor: UC Davis; Principal Investigator: Kent Pinkerton; Project Status: Completed.
The California Environmental Protection Agency has been charged with reviewing the ambient air quality standards for PM and sulfates to ensure they are protective of children. Toxicology studies provide a critical component of the overall standards review process. Toxicology studies can provide information essential for identifying which components or characteristics of PM air pollution may be more harmful or more closely associated with the adverse health effects seen in epidemiological studies of human populations exposed to ambient levels of PM. Toxicology studies can also provide valuable information on the biological mechanisms involved in causing adverse health effects in animals and humans exposed to PM. This report provides a critical review of the peer reviewed toxicology literature as it pertains to PM and PM component exposure. It is not an exhaustive summary of all toxicology studies conducted using PM or PM components. The report reflects a focused effort to examine the results of toxicology studies that the authors believe will be most helpful in addressing the ongoing air quality standards review in California. As of the completion of this report in 2002, the majority of the toxicology studies reviewed found associations between exposure to PM of many different sizes and compositions resulted in direct effects on the respiratory tract. These effects include general as well as site specific cell and tissue injury, increased production

of inflammatory biochemical species leading to increased pulmonary inflammation, increases in airway tissue reactivity leading to exacerbation of existing respiratory conditions, typically in compromised animal models. Changes have also been noted in immune cell populations or function that may lead to increased host susceptibility to respiratory infections.

A copy of the report, published in May 2002, is available at:

<http://www.arb.ca.gov/research/apr/past/00-327.pdf>.