

Final Report on the US Environmental Protection Agency Center for Ambient Particle Health Effects at Harvard

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List of Abbreviations

ACE	Angiotensin converting enzyme
AER	Air exchange rate
BAL	Bronchoalveolar lavage
BC	Black carbon
BMI	Body mass index
CAPs	Concentrated ambient particles
CB	Chronic bronchitic
CO	Carbon monoxide
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
DBP	Diastolic blood pressure
EC	Elemental carbon
ECG	Electrocardiogram
eNO	Exhaled nitric oxide
FBG	Fasting blood glucose
HAPC	Harvard/EPA Ambient Particle Concentrator
HF	High frequency power measure of heart rate variability
HRV	Heart rate variability
IQR	Inter-quartile range
LF	Low frequency power measure of heart rate variability
MI	Myocardial infarction
MSHA	Mount St. Helen's volcanic ash
NAC	N-acetyl cysteine
NAS	Normative Aging Study
Nn	Numerical density of neutrophils
NN	Normal-to-normal beat intervals for heart rate
NO	Nitric oxide
NO ₂	Nitrogen dioxide
NRC	National Research Council
O ₃	Ozone
OC	Organic carbon
PC _{0.3-1.0}	Particle counts for size range 0.3 – 1.0 µm
PM _{2.5}	Particulate matter less than 2.5 µm in diameter
PMN	Polymorphonuclear neutrophil
PVC	Premature ventricular complexes
r-MSSD	Square root of the mean of the squared differences between adjacent NN intervals
ROFA	Residual oil fly ash
SAM	Stationary ambient monitor
SBP	Systolic blood pressure
SDNN	Standard deviation of NN intervals
SO ₂	Sulfur dioxide

List of Abbreviations cont'd

SO ₄ ²⁻	Particulate sulfate
SOA	Secondary organic aerosol
SRM	Standard Reference Materials
SVA	Supraventricular arrhythmias
TP	Total power measure of heart rate variability
WBC	White blood cell

List of Principal Investigators

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US Environmental Protection Agency Center for Ambient Particle Health Effects at Harvard

Project Period

June 1, 1999 – May 31, 2006 (not cost extension June 1st 2005 - May 31st 2006)

Period Covered by the Report

June 1999 – May 2006

Overview

The US Environmental Protection Agency (EPA) Center for Particle Health Effects at Harvard worked to address key scientific issues regarding the health effects of ambient particles. The overall strategy of this Center was to build upon both our previous and ongoing research on particle health effects. The aims of the Center reflected the National Research Council's (NRC's) ten highest research priorities for ambient particle research (NRC, 1998). To meet these objectives, the Center focused on the three research themes: Exposure, Susceptibility and Biological Mechanisms/Dosimetry. We also made significant methodological advances to improve our abilities to conduct exposure and health effects studies. Over the five years the EPA Center supported a large interdisciplinary research group that collaborated intensively to investigate the health effects of ambient PM, in accordance with the NRC's research priorities for ambient particle research. Collectively, our projects addressed eight out of the ten research priorities included in the NRC report.

Exposure relationships. A large data set on personal exposures and indoor and outdoor concentrations was collected for panels of susceptible individuals across the US (Sarnat, JA et al. 2000, Sarnat, JA et al. 2001, Sarnat, JA et al. 2002). These investigations suggest that personal exposures to particulate matter less than 2.5 μm ($\text{PM}_{2.5}$) of ambient origin are highly correlated with outdoor concentrations. However, the regression slopes of personal exposures on outdoor concentrations, which are usually less than one, vary substantially depending on house characteristics, season and city climatic conditions. The strong correlations between personal and ambient concentrations were unique to $\text{PM}_{2.5}$, as personal exposures to ozone (O_3), sulfur dioxide (SO_2) and nitrogen dioxide (NO_2) were substantially lower than, and weakly correlated with, corresponding outdoor concentrations (Sarnat, JA et al. 2005).

Susceptible populations. Our epidemiological studies have provided strong evidence that individuals with congestive heart failure, chronic obstructive pulmonary disease (COPD), and diabetes are at higher risk than healthy individuals (Braga et al. 2000, Dockery 2001, Hong et al. 2002, Schwartz et al. 2003, Schwartz and Bateson 2004, Zanobetti and Schwartz 2002, Zanobetti et al. 2003). In an effort to understand why individuals with certain diseases are at greater risk

than others, Center researchers exposed animals with cardiopulmonary diseases such as COPD and myocardial infarction to concentrated ambient particles (CAPs)(Batalha et al. 2002,Clarke et al. 2000). The findings of these toxicological studies support those of the epidemiological studies and provide insight about possible mechanisms responsible for the observed particulate matter (PM) effects.

Toxic components. Many of our CAPs animal toxicology and human panel studies have linked pulmonary and cardiovascular health outcomes to different PM components such as trace metals, elemental carbon, sulfates and silicon (Batalha et al. 2002,Clarke et al. 2000, Saldiva et al. 2002). Reanalysis of the Harvard Six Cities study provided strong evidence of increased toxicity associated with combustion-related PM from traffic and power plants compared to soil dust (Laden et al. 2000).

Biological mechanisms. We have conducted exposure studies designed to elucidate the biological mechanisms whereby PM can induce adverse health effects. Results from a series of human and animal studies showed that exposures were linked to changes in heart rate variability (HRV), arrhythmias, pulmonary inflammation and vascular dysfunction (Adamkiewicz et al. 2004, Clancy et al. 2002,Clarke et al. 2000, Goodman et al. 2004, Peters et al. 2001).

Methodological issues. New statistical and epidemiological methods were developed to provide the necessary tools to address challenging PM issues such as: harvesting (Schwartz 2001, Zanobetti et al. 2000c, Zanobetti et al. 2003); confounding (Schwartz and Coull 2003); dose-exposure relationships (Schwartz 2000a, Schwartz and Zanobetti 2000, Schwartz 2001, Schwartz et al. 2002); gaseous co-pollutants; and weather confounding (Braga et al. 2000, Braga et al. 2001, Goodman et al. 2004, O'Neill et al. 2003a, O'Neill et al. 2003b, O'Neill et al. 2003c, O'Neill et al. 2004). Many new exposure and monitoring particle technologies were also developed under the aegis of our Center and are currently used worldwide. These include the ultrafine particle concentrator, the toxicological samplers, the miniature multi-pollutant sampler, the personal cascade impactor and the membrane diffusion denuder (Demokritou et al. 2002b, Demokritou et al. 2002a, Demokritou et al. 2003, Demokritou et al. 2002c, Demokritou et al. 2001a, Demokritou et al. 2002d, Demokritou et al. 2001b, Demokritou et al. 2004a, Demokritou et al. 2004b).

Introduction

The US Environmental Protection Agency (EPA) Center for Particle Health Effects at Harvard worked to address key scientific issues regarding the health effects of ambient particles. The aims of the Center reflected the National Research Council's ten highest research priorities for ambient particle research (NRC, 1998). To meet these objectives, the Center focused on the following three research themes: Exposure, Susceptibility, and Biological Mechanisms/Dosimetry. Theme I (Exposure) investigated human exposures to particles and gaseous co-pollutants in order to differentiate the health effects of particles from outdoor and indoor sources. This theme also quantified the effect of exposure error for fine particles and their co-pollutants on risk estimates from epidemiological studies. Theme II (Susceptibility) used innovative methods to identify individuals who are sensitive to the effects of air pollution, assessed whether these individuals are "harvested" by air pollution episodes, and measured the effect of chronic air pollution exposure on the development of chronic diseases. Through studies of animal and human subjects, Theme III (Biological Mechanisms/Dosimetry) identified the particulate components, or characteristics, and gaseous air pollutants that trigger adverse health effects, as well as differentiated biological mechanisms that may lead to fatal outcomes. Collectively, our projects addressed eight out of the ten research priorities included in the NRC report.

By building the Center around the three defined research themes, we maintained both a common focus and an integrated approach, which enabled us to address key issues relating to the health effects of ambient particles. These three themes included projects that spanned several disciplines in which our investigators have expertise. Our investigative group has been collaborating on particle health effects research for more than fifteen years.

The overall strategy of this Center was to build upon both our previous and ongoing research on particle health effects. This enabled us to maximize the use of data and resources in order to obtain the most useful scientific information to meet our objectives. We used data from previous epidemiological studies, as well as personal exposure measurements from more recent investigations as the basis for certain projects. The mechanistic and dosimetric studies were conducted in conjunction with our inhalation studies. As a result, the ambitious research portfolio outlined in this proposal was both timely and cost-effective.

Over the five years the EPA Center supported a large interdisciplinary research group that collaborated intensively to investigate the health effects of ambient PM, in accordance with the National Research Council's research priorities for ambient particle research. Center research produced more than 100 peer-reviewed publications (see publications list at the end of this document). While there were a large number of individual projects conducted under the EPA Center program, this report highlights several projects in each study theme.

Quality Assurance

Table 1 lists all Center sponsored projects with active human subjects' protocols. HSPH requires researchers to keep protocols active until all research activity is complete, including manuscript preparation, or until the existing data sets for the project have been de-identified.

Quality assurance project plans are on file for all research projects under the Center in which data collection took place. For projects using external data or for projects generating no internal data quality assurance checks were conducted following the guidelines outlined in the Standard Operating Manual. This manual documents the collaborative academic process through which hypotheses are developed; data sets are identified; and analysis methods are developed. These studies are usually designed and refined through an iterative process. The Standard Operating Manual documents the quality control and quality assurance steps that are an inherent part of this process from study conception through final report preparation.

Table 1: Harvard EPA Particle Center Sponsored Projects with Active Human Subjects Protocols

Protocol No.	Study Name	IRB w/ jurisdiction	Date of Last Review
P01079 0011 PART	Particulate Air Pollution Exposure Helen Suh, PI Petros Koutrakis, PI	HSPH	Nov 21, 2006
P10442 9905 ASSE	Assessing Human Exposures of High-Risk Sub-Populations to PM Petros Koutrakis, PI	HSPH	April 3, 2006
	Normative Aging Study Pantel Volkonas, PI	VA	May 22, 2006
P10530 9905 EPAP	Chronic Effects of Exposure to PM Douglas Dockery, PI	HSPH	April 28, 2006
P10069 0109 TRAF	Traffic-Related Particles and Cardiovascular Health in St. Louis H. Suh, PI P. Koutrakis, PI	HSPH Channing	Oct 22, 2006 Feb 3, 2006
P10039 0005 CARD 9710 CARD	Cardiovascular Vulnerability to Particulate Pollution Diane Gold, PI (Steubenville, age 65+)	HSPH-Suh HSPH-Gold Channing	May 18, 2006 Oct 22, 2006 July 05, 2006

THEME I: ASSESSING PARTICLE EXPOSURES FOR HEALTH EFFECTS STUDIES

A large data set on personal exposures and indoor and outdoor concentrations was collected for panels of susceptible individuals across the US (Sarnat, JA et al. 2000, Sarnat, JA et al. 2001, Sarnat, JA et al. 2002, Koutrakis et al. 2005). These investigations suggest that personal exposures to PM_{2.5} of ambient origin are highly correlated with outdoor concentrations. However, the regression slopes of personal exposures on outdoor concentrations, which are usually less than one, vary substantially depending on house characteristics, season, and city climatic conditions. The strong correlations between personal and ambient concentrations were unique to PM_{2.5}, as personal exposures to O₃, SO₂ and NO₂ were substantially lower than, and weakly correlated with, corresponding outdoor concentrations (Sarnat, JA et al. 2005).

The primary focus of Theme I was to assess human exposures to particles and gaseous co-pollutants in order to better understand their health effects. As such, research conducted as part of Theme I contained five main objectives:

- (1) to characterize the inter- and intra- variability in personal particulate and gaseous exposures;
- (2) to identify factors affecting the relationship between personal exposures and outdoor levels;
- (3) to determine the contribution of outdoor and indoor particles to personal particulate exposures;
- (4) to quantify the effect of measurement error for fine particles and their co-pollutants (coarse mass and the criteria gases) on risk estimates from epidemiological studies; and
- (5) to differentiate the health effects of particles from outdoor and indoor sources.

These objectives were addressed by three inter-related research projects, which made use of our database of personal, indoor, and outdoor particulate and gaseous exposures.

Theme I Project Ia: Assessing Human Exposures to Particulate and Gaseous Air Pollutants

Investigators:

Petros Koutrakis, Helen, Suh, Jeremy Sarnat, Kathleen Ward Brown

Institution:

Harvard School of Public Health

Description and Objectives of Research:

A central research objective of this group of projects was the examination of relationships between ambient particles and gases and corresponding personal exposures. The primary objectives of this work were to characterize exposures to PM_{2.5} and its major components and to assess the relative importance of several error sources to our ability to estimate exposures from ambient fine particle concentrations. These objectives were addressed using measurements of personal particulate exposures and corresponding indoor, outdoor, and ambient concentrations that were made for several cohorts of sensitive individuals. These data were specifically used to examine the impact of geographic location on the relationships between personal particulate and gaseous exposures; to evaluate the ability of ambient, home outdoor and home indoor pollutant concentrations to serve as proxies of personal exposure; and to determine how housing characteristics and activity patterns affect the relationships between personal exposures and ambient concentrations. The current findings indicate that geographical differences, ventilation of the home, time spent outdoors and local traffic sources may affect the ability of ambient concentrations to serve as proxies for personal exposures.

Summary of Findings/Accomplishments:

Pooling results from the Boston and Baltimore panel studies, we assessed whether the contribution of ambient particles on personal exposures varied by city, season and cohort. No cohort effect was found on the attenuation factors, which suggests that subjects from each cohort (i.e., seniors, children, COPD patients) were exposed to the same fraction of ambient PM_{2.5}, given the same concentrations of ambient PM_{2.5}. A report detailing these findings was published in 2005 (Koutrakis et al. 2005). In one paper, we analyzed data from a Baltimore multiple pollutant exposure assessment to examine the role of ambient pollutant concentrations in PM_{2.5} epidemiologic models (Sarnat, JA et al. 2001). Since the Baltimore analysis was the first to examine relationships between personal exposures and ambient concentrations for PM_{2.5} and gaseous pollutants, it was important to conduct a similar analysis for other cities. We conducted an analysis including personal exposure and ambient concentration multi-pollutant data from the

Boston panel study. Results from the Boston analysis, which includes both data from Baltimore and Boston, provide further evidence that the ambient gaseous pollutant concentrations are better surrogates of personal PM_{2.5} exposures, especially personal exposures to PM_{2.5} of ambient origin, than their respective personal exposures. These findings suggest that using ambient gas concentrations in multiple-pollutant health effects models along with PM_{2.5} may not be appropriate, since both the ambient gaseous and PM_{2.5} concentrations are serving as surrogates for PM_{2.5} exposures. In addition, the robustness of these findings was demonstrated by using various analytical methods and model structures. A paper entitled, "Relationships among Personal Exposures and Ambient Concentrations of Particulate and Gaseous Pollutants and their Implications for Particle Health Effects Studies," was published in April 2005 in Epidemiology.

An additional panel study conducted in Boston found ambient particulate sulfate (SO₄²⁻) to be strongly correlated with corresponding personal exposures and home indoor concentrations for individuals not using humidifiers, a source of indoor SO₄²⁻. Correlations between ambient SO₄²⁻ and personal exposures, however, varied by subject and by season. Associations with outdoor SO₄²⁻ concentrations were similar to those for ambient concentrations. Ambient elemental carbon (EC) and PM_{2.5} concentrations were more weakly associated with corresponding personal and indoor levels, as compared to SO₄²⁻, likely due to the contributions of indoor and other local EC and PM_{2.5} sources.

In addition, this study found infiltration of outdoor pollutants into the home to be a key factor determining the contribution of ambient pollution to personal exposures, due to the large proportion of time individuals spend in their residences. High indoor-outdoor SO₄²⁻ correlations indicated that home indoor and home outdoor levels correlated consistently regardless of the differences in the absolute levels in the two microenvironments. The significantly weaker associations for EC and PM_{2.5} compared to SO₄²⁻ indicate that personal and household activities likely play an important role in determining personal exposures and can weaken associations with outdoor or ambient concentrations.

For EC, substantial spatial variation in outdoor concentrations was found, with this spatial variation lessening the ability of ambient concentrations to act as proxies of personal EC exposures. These results suggest that placement of outdoor EC monitors closer to participants' homes may reduce exposure error in epidemiological studies of EC and other traffic-related particles. Infiltration was also shown to impact the ability of ambient concentrations to reflect exposures, as a strong seasonal difference in infiltration was found, where greater ventilation during the summer may have resulted in significantly higher personal exposures to particles originating from ambient sources. In contrast in the winter, lower infiltration can result in a greater contribution of indoor sources to personal exposures to EC and PM_{2.5}.

A number of exposure and source factors were also found to affect personal exposures, particularly ventilation, time spent outdoors, time spent in transit and proximity to a major roadway. As indicated in previous panel studies, ventilation was a significant exposure modifier primarily during summer with open windows in the home approximately doubling the personal-ambient slopes for all pollutants, except NO₂. While ventilation increased exposures to pollutants generated outdoors, there was evidence in this study of large impacts from indoor sources particularly at low ventilation rates. Subjects that spent more than an hour outdoors during

summer had significantly increased personal exposures compared to individuals that spent less than that time outdoors, but the overall effect on personal exposures differed by pollutant with the greatest difference seen for EC. Living close to a major road was associated with higher traffic-related pollutants—EC, PM_{2.5} and NO₂. This study also associated humidifiers using tap water with the highest personal and indoor SO₄²⁻ and PM_{2.5} levels measured in the study. Other residence-specific location factors, including traffic density, population density, and percent urban land use, were not significant modifiers of the personal-ambient association for any of the pollutants.

This analysis also indicated that open window status provided more consistent model results than air exchange rate (AER) in this study. The inconsistent results for AER may be due to the fact that many of the homes measured were apartments. As a result, the AER method could not differentiate between make-up air from outdoors or from neighboring apartments. Imprecision in the AER method also cannot be ruled out as contributing to this finding. As a result, future studies that include personal or indoor exposure measures may consider open windows as a better indicator of air exchange with outdoors in apartments or multi-unit buildings over a 24-hour period.

The results also indicated that infiltration into homes during the one-week monitoring period was remarkably consistent, given the various housing types measured. While the inter-home variability in infiltration ratios was substantial, infiltration ratios for a given home varied little over the week. Minimal intra-home variation in infiltration ratios is important given the complexity and difficulty of conducting large-scale personal exposure studies. A better understanding of how some housing, activity and source factors affect personal-ambient relationships may allow us to better estimate personal exposures in future health assessment studies.

Conclusions:

Determining how well ambient monitors estimate personal exposures is especially important, given the recent generation of combined health and exposure studies on small panels of individuals. For these studies, more accurate estimates of exposures are needed to provide sufficient power to examine PM-associated impacts on intermediate health outcomes, such as heart rate variability and blood inflammation markers (Dubowsky et al. 2006). In addition to assessing ambient concentrations, an assessment of ventilation conditions in the homes will likely provide a good indicator of the amount of outdoor pollution contributing to exposures in these studies.

Publications:

1. Sarnat, J., K. Brown, J. Schwartz, B. Coull and P. Koutrakis (2005). "Ambient Gas Concentrations and Personal Particulate Matter Exposures: Implications for Studying the Health Effects of Particles." *Epidemiology* 16(3): 385-395.

2. Sarnat JA, Long C, Koutrakis P, Coull BA, Schwartz J, Suh HH. Using sulfur as a tracer of outdoor fine particulate matter. *Environmental Science & Technology* 2002; 36: 5305-5314.
3. Sarnat JA, Schwartz J, Catalano P, Suh HH. Gaseous Pollutants in Particulate Matter Epidemiology: Confounders or Surrogates? *Environmental Health Perspectives* 2001; 109:1053-1061.
4. Sarnat JA, Koutrakis P, Suh H. Assessing the Relationship between Personal Particulate and Gaseous Exposures of Senior Citizens Living in Baltimore. *Journal of the Air and Waste Management Association* 2000; 50:1184-1198.
5. Sarnat SE, Coull BA, Schwartz J, Gold DR, Suh H. Factors Affecting the Association between Ambient Concentrations and Personal Exposures to Particles and Gases. *Environmental Health Perspectives* 2006; 114(5):649-654.
6. Sarnat SE, Coull BA, Ruiz P, Koutrakis P, Suh HH. The influences of ambient particle composition and size on particle infiltration in Los Angeles, CA, residences. *Journal of the Air & Waste Management Association* 2006; 56(2): 186-196.

Theme I Project Ib: Quantifying Exposure Error and its Effect on Epidemiological Studies

Investigators:

J. Sarnat, J. Schwartz, H. Suh, A. Zanobetti

Institution:

Harvard School of Public Health

Description and Objectives of Research:

The main objective of this project was to quantify exposure error and to investigate its effect on the observed associations between exposure and health outcome.

Summary of Findings/Accomplishments:

As mentioned above, the preliminary findings of Project Ia suggest that home characteristics, particularly home ventilation, are the primary determinant of the fraction of outdoor particles that penetrate indoor environments and thus are an important determinant of personal exposures to particles of outdoor origin as well. Through its impact on exposures to particles of outdoor origin, it is possible that home ventilation may also affect the association between outdoor particle concentrations and health risk. To test this hypothesis, we used data from 14 cities located across the US to examine the relationship between air conditioning prevalence and the coefficient for the relationship between ambient PM₁₀ concentrations and cause-specific hospital admissions (Janssen et al, 2002). In addition, we examined whether observed variability in the risk coefficients was specifically related to PM₁₀ emissions from mobile, combustion, and other sources.

Our research examined the impact of exposure-related factors on risk estimates from time-series studies of PM₁₀ and hospital admissions. In a paper published in 2002, we used data from 14 cities located across the US to examine the relationship between air conditioning prevalence and the coefficient for the relationship between ambient PM₁₀ concentrations and cause-specific hospital admissions (Janssen et al, 2002). In addition, we examined whether observed variability in the risk coefficients was specifically related to PM₁₀ emissions from mobile, combustion, and other sources. Results from this study indicate that air conditioning use explains a substantial amount of the variability in the risk coefficients from the different cities. Furthermore, PM₁₀ emissions from mobile and diesel sources were also found to be important determinants of the variability in the risk coefficients, particularly for CVD-related hospital admissions. To validate these findings, we used the same data to examine whether ventilation and source emission

profiles explain season-specific risks of PM₁₀ on hospital admissions in each of these 14 cities. This analysis is nearly complete, but a paper has not been submitted for review.

As part of our work to assess exposure error, we developed new methods to correct for measurement error in hierarchical models (Schwartz and Coull 2003). We showed that existing standard two-stage estimators will be biased in the presence of exposure measurement error and that this bias can be away from the null hypothesis of no effect. We proposed two alternative methods for estimating the independent effects of two predictors in a hierarchical model. We applied the new methodology to show that the estimated effect of fine particles on daily deaths, independent of coarse particles, was downwardly biased by measurement error in an original analysis that did not correct for measurement error. We also used the methods to estimate the effect of gaseous air pollutants on daily deaths. The resulting effect size estimates were very small and the confidence intervals included zero. We applied this approach to a reanalysis of the NMMAPS mortality study conducted by Johns Hopkins University researchers, which was published as a report to the Health Effects Institute (HEI, 2003). Also, using data from multi-pollutant exposure studies in Boston and Baltimore, simulations were conducted to assess the feasibility of health risks attributed to gases and particles. Results provided evidence that the gaseous pollutants are unlikely confounders of PM health risk estimates for these locations. These results were presented in a meeting abstract (Schwartz and Sarnat 2002), and a manuscript has been submitted to the Journal of Exposure Science and Environmental Epidemiology.

We have also been working on the development and application of near-source and long-range atmospheric dispersion models to better quantify the relationship between emissions and concentrations of primary and secondary PM. This analysis will allow for improved spatially resolved exposure estimates and reduced exposure misclassification. A paper is under preparation, but it has not been finalized for submission.

Spatial-Temporal Modeling of Exposure. We developed spatial-temporal models of spatially varying exposures, such as traffic pollution, in the Boston area. Given a good model for exposure, this approach yields more accurate measures of spatially heterogeneous exposures than central site monitoring, and allows for examination of longer averaging times than the limited personal exposures. This approach can decrease the amount of measurement error associated with the central-site measurements and in turn yield more powerful tests of health effects. This manuscript was published. A revised manuscript describing the methodology and results of this analysis has been accepted by the Journal of Royal Statistical Society (Gryparis et al. 2007).

Quantifying Model Uncertainty in Epidemiological Analyses. A criticism of existing PM epidemiologic analyses is the multiple sources of uncertainty involved in obtaining health effect estimates. One key uncertainty is the shape of the concentration-response relation. Another is estimating how long one would have to wait after lowering pollution before the health improvements arrive. That is, are the associations with twenty-year average exposures, which will change slowly, or are they with recent exposures? We examined the use of Bayesian model averaging as a way of addressing these two forms of model uncertainty in a reanalysis of the Harvard Six Cities study. This approach avoids relying on an effect estimates from a single “final” model, which ignores uncertainty associated with model choice and thus can underestimate the variability associated with these effect estimates. Rather this method takes a

weighted average of estimates from a range of plausible models. We implemented this approach to average over plausible models for the dose-response relationship of PM as well as the lag structure in the model. Preliminary results suggest that the dose-response curve is approximately linear and the strongest lagged effects occur during the current year (i.e. lag 0) and the immediately preceding year (i.e. lag 1). A paper describing the analysis has been submitted and is currently under review.

Conclusions:

Results from our work indicate that air conditioning use explains a substantial amount of the variability in the relationship between ambient PM₁₀ concentrations and cause-specific hospital admissions from 14 different cities studied. Additional results provided evidence that gaseous pollutants are unlikely confounders of PM health risk estimates. Finally, our results suggest that the dose-response curve for PM health effects is approximately linear, and the strongest lagged effects occur during the current year (i.e. lag 0) and the immediately preceding year (i.e. lag 1).

Publications:

1. Janssen NAH, Schwartz J, Zanobetti A, Suh H. Air Conditioning and Source-Specific Particles as Modifiers of the Effect of PM₁₀ on Hospital Admissions for Heart and Lung Disease. *Environmental Health Perspectives* 2002; 110:43-49.
2. Schwartz J. Is the Association of Airborne Particles with Daily Deaths Confounded by Gaseous Air Pollutants? An Approach to Control by Matching. *Environmental Health Perspectives* 2004; 112(5):557-561.
3. Schwartz J, Coull BA. Control for Confounding in the Presence of Measurement Error in Hierarchical Models. *Biostatistics* 2003, 4(4):539-53.
4. Schwartz J, Sarnat JA. Effects of measurement error on associations between ambient air pollution and daily mortality: A simulation study using the covariance of personal and ambient measurements. *Epidemiology* 2002; 13(4): 081.

Theme I Project Ic: The St. Louis Bus Study

Investigators:

G. Adamkiewicz, S. Dubowsky, D. Gold, S. Sarnat, H. Suh

Institution:

Harvard School of Public Health

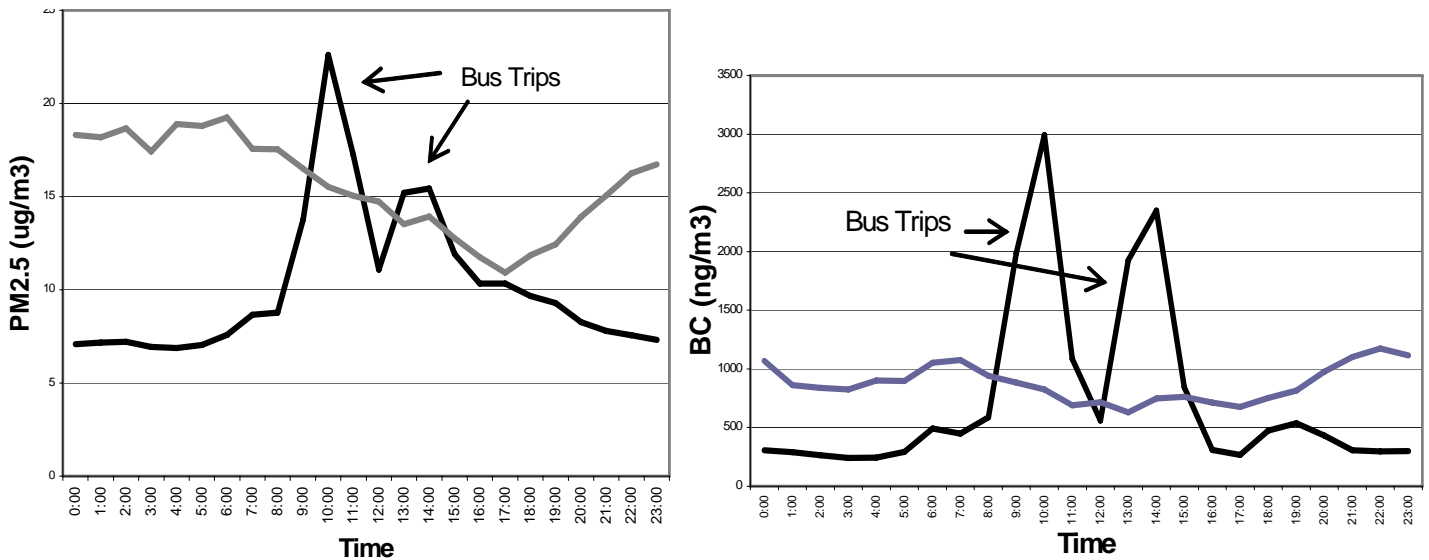
Description and Objectives of Research:

As part of Theme 1, we conducted a particle exposure and health effects study that specifically focused on the health effects of traffic-related pollutant exposures. This study examined the effects of ambient and traffic related pollution on intermediate cardiovascular and inflammatory health markers, including heart rate variability (HRV), systemic inflammation and pulmonary inflammation. The field study was conducted in St. Louis, MO during Spring 2002. We monitored the cardiovascular health of 44 individuals living in retirement facilities in metropolitan St. Louis, MO as they traveled on field trips aboard a diesel-powered bus. Markers of altered cardiovascular function including heart rate variability, heart rate, inflammatory indicators in the blood, and oxygen saturation of the blood were measured for participants during four separate 24-hr periods as the individuals traveled between the health testing room, a moving shuttle bus, indoor locations within the city, and his or her senior residence facility. Micro-environmental PM_{2.5}, black carbon (BC) and fine particle count (PC_{0.3-1.0}) exposures were assessed continuously for the study participants using two portable monitoring carts that traveled with the study participants throughout the day. The EPA-funded St. Louis Super Site served as the stationary ambient monitoring (SAM) site for measuring ambient concentrations.

Summary of Findings/Accomplishments:

Particle Exposures. As shown in Figure 1, personal exposures to PM_{2.5}, BC and PC_{0.3-1.0} were significantly higher when participants were aboard the diesel-powered shuttle bus as compared to when they were in their residence facilities ($p < 0.001$). Exposures were the most elevated for BC. It can be assumed that elevated exposures during bus trips were attributed to emissions from surrounding vehicles and the shuttle bus, since mean concentrations at the SAM site during the bus and facility periods were comparable.

Figure 1. Hourly Micro-environmental and Ambient PM_{2.5} and BC Concentrations. Microenvironmental PM_{2.5} (left) and BC (right) exposures were measured as participants traveled on a field trip via two bus rides and spent time in their residence facility. Micro-environmental exposures are shown in black; ambient concentrations are shown in grey. Exposures and concentrations were averaged by hour.



Heart Rate Variability. Exposure to airborne particles may increase cardiac risk by altering autonomic balance. As these risks may be particularly great for traffic-related particles, we examined associations between particles and heart rate variability for 44 subjects who participated in four repeated trips aboard a diesel bus. Twenty-four hour electrocardiograms were correlated with continuous particle concentrations using generalized additive models controlled for subject, weekday, time, apparent temperature, trip type, activity, medications, and autoregressive terms. Associations were assessed for short and medium-term mean concentrations.

Heart rate variability was significantly and negatively associated with fine particulate matter. Significant positive associations were demonstrated with heart rate and the low to high frequency power ratio. Associations were strongest with 24-hour mean concentrations although strong and significant short-term associations also were found during bus periods, independent of daily exposures. Overall, associations were largest for high frequency power with 16 (95% CI: -17, -15), 19 (95% CI: -22, -17), and 14 (95% CI: -16, -13) percent decreases per inter-quartile changes in the 24-hour PM_{2.5} ($4.6 \mu\text{g}/\text{m}^3$), black carbon ($458 \text{ ng}/\text{m}^3$), and fine particle count ($39 \text{ pt}/\text{cm}^3$) concentrations, respectively. Eleven percent (95% CI: -13.6, -7.8) decreases in high frequency power were predicted per inter-quartile change in the 5-minute PM_{2.5} ($10 \mu\text{g}/\text{m}^3$) aboard the bus. This investigation indicates that fine particles are negatively associated with heart rate variability, with an overall trend towards reduced parasympathetic tone. While daily associations were evident for all particles, short-term associations were predominantly limited to bus periods and possibly fresh traffic-related particles. These findings were published in *Epidemiology* (Adar et al. 2007b).

Systemic Inflammation. Inflammation may represent a pathway through which airborne particles lead to increased cardiac risk. Therefore, we investigated associations between ambient particles and acute systemic inflammation among repeated measures of 44 seniors and examined susceptibility by conditions linked to chronic inflammation. Mixed models were used to identify associations between fine particle concentrations (PM_{2.5}) averaged over 1 to 7 days and measures of C-reactive protein (CRP), interleukin-6 (IL-6), and white blood cell counts (WBC). Effect modification was investigated for diabetes, obesity, hypertension, and elevated mean inflammatory markers.

Positive associations were consistently found between ambient PM_{2.5} and WBC across all participants, with an 11% (95% CI: 0.19 to 22%) increase per 10 µg/m³ increase in PM_{2.5} averaged over the previous week. PM_{2.5} and CRP also exhibited positive associations among all individuals for averaging periods longer than 1 day with the strongest associations for persons with diabetes, obesity, and hypertension. For example, a 10 µg/m³ increase in the 5 day mean PM_{2.5} was associated with a 24% increase in CRP (95% CI: -8.8 to 67%) for all individuals and a 170% (95% CI: 36 to 420%) increase for persons with diabetes, obesity, and hypertension. Persons with diabetes, obesity, and hypertension also exhibited positive associations between PM_{2.5} and IL-6. Individuals with elevated mean inflammatory markers exhibited enhanced responsiveness for CRP, IL-6, and WBC. This investigation demonstrates that air pollution is positively associated with acute systemic inflammation and indicates enhanced sensitivity for individuals with diabetes, obesity, hypertension, and elevated mean inflammatory markers. These findings were published in *Environmental Health Perspectives* (Dubowsky et al. 2006).

Pulmonary Inflammation. Airborne particles have been linked to pulmonary oxidative stress and inflammation. As these effects may be particularly great for traffic-related particles, we examined associations between particle exposures and exhaled nitric oxide (eNO), a marker of pulmonary inflammation. Samples of eNO collected before and after the trips were correlated with micro-environmental and ambient particle concentrations using mixed models controlled for subject, day, trip, vitamins, collection device, mold, pollen, room air nitric oxide, apparent temperature, and time to analysis. While ambient concentrations were collected at a fixed location, continuous group-level personal samples characterized micro-environmental exposures throughout facility and trip periods. Findings from this analysis have been published in *Environmental Health Perspectives* (Adar et al. 2007a).

Briefly, we found eNO concentrations collected prior to participation in a bus trip to be significantly associated with PM_{2.5} and PC_{0.3-1.0} averaged over the previous 24-hrs. For example, an inter-quartile increase in the 24-hr mean ambient PM_{2.5} of 10 µg/m³ resulted in a 15% (95%CI: 6 – 26%) increase in eNO using linear models adjusted for day of week, ambient apparent temperature, past nitrate consumption, recent meal, time between sample collection and analysis, study room nitric oxide (NO) concentrations, and a random subject effect. A similar increase for personal PM_{2.5} (as measured by the portable monitoring carts inside the facility) corresponded to a 20% (95%CI: 1 – 43%) increase in eNO, while an inter-quartile range (IQR) change in PC_{0.3-1.0} of about 70 pt/cc resulted in 30% increase in eNO (95%CI: 1 – 43%). Changes in BC, carbon monoxide (CO), NO, and NO₂ were not significantly associated with deviations in eNO at the 95% confidence level.

On the day following the bus trip, we found similar effect estimates for measures of micro-environmental PM_{2.5} (20%, CI: 6-35%) and PC_{0.3-1.0} (23%, CI: 8-40%) when identical models were used. While ambient PM_{2.5} was predictive of eNO when participants were at their living facilities for the previous 24-hr, ambient PM_{2.5} was not predictive of eNO when the same individuals took part in a field trip that included two hours on the highway. While the gases remained non-predictive of post-trip eNO, BC became a significant predictor of eNO (20%, CI: 2-40%) for samples collected on the days after the bus trips. Data suggest that elevated exposures to traffic-related particles result in increased pulmonary inflammation as measured by eNO. Future findings will refine our analyses of the effects of motor vehicle exposures on eNO and determine whether autonomic effects such as HRV, ST-segment depression, and arrhythmias are also associated with motor vehicle exposures, as this was shown in a previous Center publication (Gold et al. 2005).

Conclusions:

These results suggest that air pollution exposures are associated with systemic inflammation among seniors having at least one symptom of metabolic syndrome, suggesting pollution impacts for a large proportion of the elderly in the U.S. (approximately 33% with obesity and 50% with hypertension). Inflammation associated with air pollution appears to occur acutely, with most effects within the first day of exposure.

This investigation also indicates that fine particles are negatively associated with heart rate variability with an overall trend towards reduced parasympathetic tone. While daily associations were evident for all particles, short-term associations were predominantly limited to traffic-related particles.

Publications:

1. Adar, SD et al 2007 Adar, S., D. Gold, B. Coull, J. Schwartz, P. Stone and H. Suh (2007). "Focused exposures to airborne traffic particles and heart rate variability in the elderly." *Epidemiology* 18(1): 95-103.
2. Adar, S., G. Adamkiewicz, D. Gold, J. Schwartz, B. Coull and H. Suh (2007). "Ambient and microenvironmental particles and exhaled nitric oxide before and after a group bus trip." *Environmental Health Perspectives* 115(4): 507-512.
3. Dubowsky SD, Suh H, Schwartz J, Coull BA, Gold DR. Diabetes, Obesity, and Hypertension may Enhance Associations between Air Pollution and Markers of Systemic Inflammation. *Environmental Health Perspectives* 2006; 114(7):992-998.
4. Gold DR, Litonjua AA, Zanobetti A, Coull BA, Schwartz J, MacCallum G, Verrier RL, Nearing BD, Canner MJ, Suh H, Stone PH. Air Pollution and ST-Segment Depression in Elderly Subjects. *Environmental Health Perspectives* 2005; 113(7):883-887.

Theme I Project 1d: Steubenville

Investigators:

B. Coull, D. Dockery, D. Gold, H. Luttmann-Gibson, S. Sarnat, J. Schwartz, P. Stone, H. Suh

Institution:

Harvard School of Public Health

Description and Objectives of Research:

We conducted a particle exposure and health effects study in Steubenville, OH (Sarnat, S. E. et al. 2006). This field study included weekly measurement of thirty two non-smoking older adults for 24 weeks during Summer and Fall 2000. Continuous electrocardiogram measurements were made for each subject using a standardized 30 minute protocol. A central ambient monitoring station provided daily concentrations of PM_{2.5}, sulfate, elemental carbon and gases.

Analysis of these results focused on: (1) the potential effects of particulate matter and gases on autonomic nervous system dysfunction and inflammation, potential pathways by which particles affect cardiac rate and rhythm; and (2) the potential effects of these pollutants on the parasympathetic and sympathetic nervous systems. For the first area of research, published by Sarnat, S. E. et al (2006), the two primary health outcomes were supraventricular ectopy (SVE), defined as extra cardiac depolarizations within the atria, and ventricular ectopy (VE) or extra depolarizations in the ventricles. For the second area of research (Luttmann-Gibson et al. 2006), the effects of the pollutants on various measures of heart rate variability (HRV) were assessed. These HRV measures included: (1) the standard deviation of normal R-R intervals in the ECG (SDNN); (2) the mean square of differences between adjacent RR intervals in the ECG (r-RMSSD); (3) high frequency (HF) power; and (4) low frequency (LF) power.

In addition, we measured the fraction of exhaled nitric oxide (FENO) in the study subjects' breath to evaluate the potential association with air pollution levels, as this metric is a non-invasive measure of airway inflammation (Adamkiewicz et al. 2004).

Summary of Findings/Accomplishments:

Participant specific mean counts of arrhythmia over the protocol varied between 0.1–363 for SVE and 0–350 for VE. The authors observed odds ratios for having SVE over the length of the protocol of 1.42 (95% CI 0.99 to 2.04), 1.70 (95% CI 1.12 to 2.57), and 1.78 (95% CI 0.95 to 3.35) for 10.0 µg/m³, 4.2 µg/m³, and 14.9 ppb increases in five day moving average PM_{2.5}, sulfate and ozone concentrations, respectively. The other pollutants, including elemental carbon, showed no effect on arrhythmia. Participants reporting cardiovascular conditions (for example,

previous myocardial infarction or hypertension) were the most susceptible to pollution induced SVE. The authors found no association of pollution with VE.

In a community with significant industrial sources for air pollution, our study demonstrated an association of particle pollution with increased odds of supraventricular arrhythmia in a cohort of older adults, with findings of 42%, 70%, and 78% increases in odds of SVE associated with IQR increases in five day moving average PM_{2.5}, sulfate and ozone, respectively. Air pollution effects were greatest for participants with a history of clinically significant cardiac disease. Since two pollutant models demonstrated stability in the effects of both particles and ozone, collectively our results may provide evidence of the combined effect of the secondary pollutant mix in Steubenville on cardiac arrhythmia. Specifically, the strong effects found with sulfate are interesting as Steubenville is located in an industrial area of the Ohio River Valley, with little traffic but with a number of coal-fired power plants, which are the major source of SO₂, a sulfate precursor. It is important to note that ambient sulfate concentrations were measured with higher overall precision, and further, that ambient sulfate concentrations were better proxies of corresponding personal exposures as compared to EC. Both factors may have resulted in sufficient power to detect associations between arrhythmia and ambient concentrations of sulfate. A previous study conducted in Boston, reporting on patients with implantable cardioverter defibrillators, found that traffic related pollutants, particularly NO₂, showed the greatest odds of arrhythmia (Peters et al. 2000). Our data suggest that pollution in an industrial location may also contribute to the risk of arrhythmia, and they indicate the potential for varying impacts of air pollution by geographical location and source contributions.

The second paper found significant reductions in HRV measures associated with increased PM_{2.5} and sulfate, but no significant reductions in HRV associated with EC, NO₂, SO₂ or O₃ levels. An interquartile range (IQR) increase in sulfate of approximately 5 ug/m³ resulted in decreases of 3.3 % for SDNN, 5.6% for r-RMSSD and 10.3% for HF with similar results for PM_{2.5}.

In addition, an increase in the 24 hour average PM_{2.5} concentration of 17.7 µg/m³ was associated with an increase in FENO of 1.45 ppb (95% CI 0.33 to 2.57) in models adjusted for subject, week of study, day of the week, hour of the day, ambient barometric pressure, temperature, and relative humidity. This represents a change of approximately 15% compared with the mean FENO in the cohort (9.9 ppb). The associations between FENO and PM_{2.5} were significantly higher in subjects with a doctor's diagnosis of COPD (p value for interaction = 0.03).

Conclusions:

Our results suggest that increased levels of ambient air pollution, particularly for regional pollutants, including sulfate and ozone, may increase the risk of supraventricular arrhythmia in the elderly. The highest and most significant effects were found for greater than five day moving average concentrations before the health assessment, which may suggest that a long acting mechanism promoted the ectopic beats in our population. Furthermore, the results suggest that individuals with a history of clinically significant cardiac disease may be at particular risk of air pollution health effects. Additional analysis found that increased levels of sulfate and PM_{2.5} may adversely affect autonomic nervous system function, resulting in significant cardiac effects.

Ambient pollution may also lead to airway inflammation as measured by FENO. These subclinical inflammatory changes may be an important step in the pathogenesis of the cardiopulmonary effects induced by exposure to air pollution.

Publications:

1. Adamkiewicz G, Ebel S, Syring M, Slater J, Speizer FE, Schwartz J, Suh H, Gold DR. Association Between Air Pollution Exposure and Exhaled Nitric Oxide in an Elderly Population. *Thorax* 2004; 59:204-209.
2. Luttmann-Gibson, H., H. H. Suh, B. A. Coull, D. W. Dockery, S. E. Sarnat, J. Schwartz, P. H. Stone and D. R. Gold (2006). "Short-term effects of air pollution on heart rate variability in senior adults in Steubenville, Ohio." *Journal of Occupational and Environmental Medicine* 48(8): 780-788.
3. Sarnat, S. E., H. H. Suh, B. A. Coull, J. Schwartz, P. H. Stone and D. R. Gold (2006). "Ambient particulate air pollution and cardiac arrhythmia in a panel of older adults in Steubenville, Ohio." *Occupational and Environmental Medicine* 63(10): 700-706.

Theme I Project 1e: Atlanta

Investigators:

D. Gold, J. Schwartz, P. Stone, H. Suh, A. Wheeler, A. Zanobetti

Institution:

Harvard School of Public Health

Description and Objectives of Research:

Associations between concentrations of PM_{2.5} and heart rate variability (HRV) have differed by study population. Results from previous studies suggested that compromised autonomic control of the heart may play a role in the acute cardiovascular toxicity of particles but that this role may differ with the underlying health status of the individual. The impact of health status on the relationship between HRV and ambient PM had not been examined directly, with previous panel studies including participants of only one susceptible disease group. To examine this issue more directly, we conducted a study to evaluate associations between ambient PM_{2.5} and HRV for sensitive individuals (Wheeler et al. 2006). We then examined whether these associations differed for individuals with preexisting pulmonary disease compared to those with cardiovascular disease.

We examined the effects of ambient pollution on HRV for 18 individuals with chronic obstructive pulmonary disease (COPD) and 12 individuals with recent myocardial infarction (MI) living in Atlanta, Georgia. HRV, baseline pulmonary function and medication data were collected for each participant on 7 days in Fall 1999 and/or Spring 2000. Hourly ambient pollution concentrations were obtained from monitoring sites in Atlanta. The association between ambient pollution and HRV was examined using linear mixed-effect models. The primary time domain HRV measures presented here include: (1) the standard deviation of normal R-R intervals in the ECG (SDNN); and (2) the square root of the mean of the sum of squares of differences between adjacent NN intervals in the ECG (RMSSD).

Summary of Findings/Accomplishments:

Ambient pollution had opposing effects on HRV in our COPD and MI participants, resulting in no significant effect of ambient pollution on HRV in the entire population for 1-, 4-, or 24-hr moving averages. Findings from our study provide direct evidence of heterogeneity in the autonomic response to ambient pollution that is dependent on the underlying health status of the study population. Changes in HRV were significantly and positively associated with ambient PM_{2.5} concentrations for individuals with COPD. Although not statistically significant, observed associations were consistently negative for individuals with recent MI. Further support that the HRV response to ambient PM_{2.5} differs for individuals with MI and COPD was provided by the

fact that we found comparable effect estimates, with significant differences between disease groups, using models that included an interaction term between pollution and disease status. Associations with ambient PM_{2.5} were strongest for the 4-hr moving average and for SDNN an overall measure of HRV, although consistent trends with disease status were observed for other moving averages and other HRV measures. We also observed strong and significant associations with SDNN by disease group with ambient NO₂, and to a lesser extent with ambient EC. Because ambient NO₂ and EC originate primarily from motor vehicles, our findings suggest that motor vehicle-related pollution may be partly responsible for the observed effects of ambient particles on HRV.

The effect of medication use, respiratory rate, baseline pulmonary function (based on FEV1), air conditioning use, exercise during HRV measurement, body mass index, age, and heart rate on the association between 4-hr ambient pollution and overall SDNN was examined to determine whether these factors was responsible for the differences in response between the disease groups. Of these, medication use and baseline FEV1 were found to be significant effect modifiers for 4-hr PM_{2.5} and NO₂ concentrations, with results comparable for the two pollutants. Similar effect modification by medication use and baseline pulmonary function was also found for EC but with smaller effect sizes.

Conclusions:

Findings from our study provide direct evidence of heterogeneity in the autonomic response to ambient pollution that is dependent on the underlying health status of the study population. Changes in HRV were significantly and positively associated with ambient PM_{2.5} concentrations for individuals with COPD. Although not statistically significant, observed associations were consistently negative for individuals with recent MI.

Publications:

1. Wheeler, A., A. Zanobetti, D. R. Gold, J. Schwartz, P. Stone and H. H. Suh (2006). "The relationship between ambient air pollution and heart rate variability differs for individuals with heart and pulmonary disease." *Environmental Health Perspectives* 114(4): 560-566.

Theme I Project 1f: Modeling Relationships between mobile source particle emissions and population exposures

Investigators:

J. Evans, S. Greco, J. Levy, J. Spengler, G. Stevens, A. Wilson

Institution:

Harvard School of Public Health

Description and Objectives of Research:

This project entailed extending our intake fraction (iF) methodology (Levy et al. 2003, Levy et al. 2002) to address motor vehicle emissions, as a way of informing PM control decisions and future analyses. Our specific objectives were to:

- Evaluate geographic patterns in primary and secondary particulate matter iFs for mobile sources, using a national-scale source-receptor (S-R) matrix;
- Determine the relative contributions of near-source and long-range populations to particulate matter iFs for mobile sources in different geographic locations;
- Develop predictive regression equations for iFs to explain geographic patterns as a function of population density and meteorological covariates

Summary of Findings/Accomplishments:

Results from this analysis were recently published (Greco et al. 2007b). For primary fine particulate matter emitted from mobile sources, the intake fractions varied across source counties from 0.14 to 23 per million (median of 1.2 per million). These values were highly correlated with near-source population density; the population in the source county explained 43% of the variability in the above estimates, and a multivariate regression model with population at various radii from the source explained 86% of the variability. Spatial analyses of residuals indicated generally strong model performance, with greater errors along the coasts, where wind fields are more difficult to characterize and downwind populations may be less significant.

For secondary ammonium sulfate formed from SO₂ emissions, the median intake fraction (0.43 per million) was somewhat lower than for primary PM. The variability was similar to that for primary PM, but with more regional variability rather than small-scale spatial variability. In spite of the regional influence on atmospheric chemistry, multivariate regressions with only population terms had an R² of 0.78, indicating the significance of population patterns even in this

context. However, there was relatively greater statistical significance for population beyond 200 km from the source, relative to primary PM, and relatively lower statistical significance for population within 200 km, reflecting expected concentration patterns.

Secondary ammonium nitrate formed from NO_x emissions had an even lower median intake fraction (0.072 per million), with spatial variability driven somewhat by population patterns (R^2 of 0.63 in multivariate regression model) but also by relative ambient concentrations of sulfate, nitrate and ammonium. Higher values tended to be found in the Midwest, where there is adequate ammonia to neutralize nitrate (and lower ambient sulfate), versus higher levels in the Ohio River Valley and Northeast for secondary sulfate and primary PM.

We also quantified the extent to which SO₂ controls might free up ammonia to react with nitrate, thereby increasing ammonium nitrate concentrations. We determined that the public health benefits of SO₂ emission controls (due to sulfate reductions) would be offset by ammonium nitrate increases by an average of 9%, ranging from 1% to 29% across U.S. counties.

As mentioned above, one of our primary objectives was to determine the relative importance of near-source and long-range populations. The median distances within which half of the total intake fraction was realized was about 150 km for primary PM, 450 km for secondary sulfate, and 390 km for secondary nitrate. However, these values varied substantially by setting (i.e., range for primary PM from 0 km, indicating that more than 50% of the iF was realized in the source county, to 1800 km). In dense urban areas, often a majority of the intake fraction was realized within the source county, indicating that more geographically resolved dispersion modeling may be warranted.

Comparing our results with the published literature, the magnitude of our estimates appear reasonable, and this analysis remains the first attempt to characterize spatial variability in mobile source intake fractions and to derive conclusions about the model scope and resolution needed to accurately estimate public health benefits of pollution control from mobile sources. Specifically, we concluded that a national-scale county-resolution dispersion model is likely sufficient for secondary particulate matter or primary particulate matter in rural areas with substantial downwind populations, but that more resolved models should be explored in dense urban areas or less-populated areas without significant downwind populations.

Based on the findings from Greco et al. 2007b we proceeded with follow-up work addressing potential within-county heterogeneity in primary PM mobile source intake fractions, as well as the questions of the spatial extent of the iF for sources within urban areas and the potential biases in estimates based on county-level resolution. We used the CAL3QHCR dispersion model (in the CALINE family of models) to simulate the influence of line-source emissions on concentrations on 23,000 road segments in the Boston area. A year's worth of hourly intake fractions were determined for each road segment using actual meteorological conditions and residential population patterns. The annual average values for the road segments range from 0.8 to 53 per million, with a mean of 12 per million. On average, 46% of the total exposure is realized within 200 m of the road segment, though this varies from 0 - 93% across road segments, largely due to variable population patterns. Our findings indicate the likelihood of substantial intra-urban variability in mobile source primary PM_{2.5} iF, especially as taking into account population

dynamics, localized meteorological conditions, and street-canyon configurations might all increase the variability in iF. These results were published as part of a doctoral thesis, and a manuscript has been submitted to Environmental Science & Technology (Greco et al. 2007a).

Conclusions:

Specifically, we concluded that a national-scale county-resolution dispersion model is likely sufficient for secondary particulate matter or primary particulate matter in rural areas with substantial downwind populations. Our findings also indicate the likelihood of substantial intra-urban variability in mobile source primary PM_{2.5} iF, especially as taking into account population dynamics, localized meteorological conditions, and street-canyon configurations might all increase the variability in iF. As a result, more resolved models should be explored in dense urban areas or less-populated areas without significant downwind populations.

Publications:

1. Greco SL, Wilson AM, Spengler JD, Levy JI. Spatial patterns of mobile source particulate matter emissions-to-exposure relationships across the United States. *Atmos Environ* 41: 1011-1025 (2007).
2. Greco, S., A. Wilson, S. Hanna and J. Levy (2007). "Factors influencing mobile source particulate matter emissions- to-exposure relationships in the Boston urban area." Submitted to Environmental Science & Technology.
3. Levy JI, Wilson AM, Evans JS, Spengler JD. Estimation of Primary and Secondary particulate matter intake fractions for power plants in Georgia. *Environ Sci & Technol* 37: 5528-5536 (2003).
4. Levy, J., S. Wolff and J. Evans (2002). "A regression-based approach for estimating primary and secondary particulate matter intake fractions." *Risk Analysis* 22(5): 895-904.

THEME II: IDENTIFYING POPULATIONS SUSCEPTIBLE TO THE HEALTH EFFECTS OF PARTICULATE AIR POLLUTION

Theme II Project IIa: Examining Conditions that Predispose Towards Acute Adverse Effects of Particulate Exposures

Investigators:

M. O'Neill, J. Schwartz, G. Wellenius, A. Zanobetti

Institution:

Harvard School of Public Health

Description and Objectives of Research:

Identification of populations that are especially susceptible to PM health effects can further our understanding of biologic mechanisms of heart and lung disease attributable to PM. This area of our work has focused on testing the hypothesis that patients with pre-existing respiratory, cardiovascular or diabetic conditions have an enhanced mortality response to particle exposures.

Summary of Findings/Accomplishments:

As part of this research effort, we previously reported that socio-economic factors were not modifiers of the risk of PM associated mortality (Zanobetti and Schwartz 2000), although there was some increased risk in females. The same pattern held true for hospital admissions for heart and lung disease (Zanobetti et al. 2000a). In contrast, we found that respiratory illness modified the risk of cardiovascular hospital admissions associated with PM (Zanobetti et al. 2000b) and that heart failure modified the risk of PM-associated COPD admissions.

Additional work by our group has shown that individuals with diabetes are at higher risk from exposure to PM. We have published several papers addressing this issue. We published two studies suggesting that diabetes is an effect modifier (Zanobetti and Schwartz 2001, 2002). One paper examined effect modification by concurrent diagnosis of diabetes overall and by age group in four US cities (Zanobetti and Schwartz 2002), concluding that individuals with diabetes have twice the risk of a PM₁₀-associated cardiovascular admission compared to those without the disease.

To further examine susceptibility by diabetes observed in these population studies, we obtained clinical information to gain insights on potential biological mechanisms. With researchers at the Joslin Diabetes Center and Beth Israel/Deaconess Hospital, we analyzed the relationship between

air pollution and both inflammation and vascular reactivity in over 200 greater-Boston residents participating in clinical trials. We used particle data (PM_{2.5}, particle number [PN], BC and SO₄²⁻) measured at the HSPH site established by the PM center. Both BC and SO₄²⁻ particles appeared to have effects on vascular reactivity and endothelial function, especially among people with diabetes. (O'Neill et al. 2005b) Additional analyses have shown associations between increased particle levels and blood markers of inflammation, including ICAM-1, VCAM-1, and von Willibrand's factor, and a manuscript has been accepted for publication in Occupational and Environmental Medicine (O'Neill et al. 2007).

We continued to explore factors influencing vulnerability to temperature-related mortality. Data on air pollution compiled for PM center projects have been used to control for confounding. In a study of seven US cities, lower educational attainment, black race, and dying outside a hospital were markers of vulnerability to death on extreme temperature days, controlling for PM₁₀ exposure. (O'Neill et al. 2003c). In a follow-up analysis, we found that air conditioning prevalence explained some of the observed racial disparities in heat-related mortality in four of these cities (O'Neill et al. 2005c). An additional analysis found that air pollution and epidemics were important confounders of temperature and mortality associations and suggested inclusion of PM₁₀, O₃, and epidemic periods in future analyses that can be used in forecasting health impacts of climate change. (O'Neill et al. 2005a).

Furthermore, we conducted mortality follow-ups of subjects whose potentially predisposing conditions were identified for use in hospital admissions data. These analyses used the case-crossover approach. We completed a methodological paper examining the potential for bias and confounding in that approach and developed new statistical methods to address these problems (Bateson and Schwartz 2001). The newly developed methods estimate and subtract biases from health risk estimates. We also conducted simulations showing our method has correct coverage probabilities, but a paper has not been submitted for review (Bateson & Schwartz, in preparation).

Mixed models are another group of analysis methods that represent an important tool for determining whether persons with certain characteristics are more susceptible to the effects of airborne particles. However, classic mixed regression programs are linear models, whereas we know that season and weather effects on health are often nonlinear. These have often been addressed using nonparametric smoothing. To enhance our ability to assess sensitivity while maintaining good covariate control, we developed an additive mixed model, which combines the attributes of both approaches (Coull et al. 2001).

The case-crossover approach was also used to examine the PM₁₀-associated risk of emergency hospitalization for myocardial infarction during 1985-1999 among elderly residents of twenty-one US cities. Results from this study showed increased risk of hospitalization for myocardial infarction for diabetics. Effect sizes were roughly doubled in persons with COPD or concurrent pneumonia compared to those without (Zanobetti et al. 2004).

More recently we examined the association of PM_{2.5} and changes in blood markers of cardiovascular risk, including lipid profiles and markers of acute systemic inflammation, in the

VA Normative Aging Study. For the same outcomes the associations were not as strong in the group taking statins (Zeka et al. 2006).

Conclusions:

A number of factors were found to increase the effects of particulate matter on morbidity and mortality. SES was not identified as a modifier of PM mortality or hospital admissions for heart and lung disease. Pre-existing respiratory illness modified the effects of PM-related cardiovascular hospital admissions, and in turn, heart failure increased the risk of PM-related COPD hospital admissions. Individuals with diabetes had double the risk of PM-related cardiovascular hospital admissions. Controlling for respiratory epidemics does not change the effect size estimates for PM on mortality. Race and SES indicators were modifiers of mortality on extreme temperature days.

Publications:

1. Bateson T, Schwartz J. Selection Bias and Confounding in Case-Crossover Analyses of Environmental Time Series Data. *Epidemiology* 2001; 12:654-661.
2. Braga AL, Zanobetti A, Schwartz J. The Effect of Weather on Respiratory and Cardiovascular Deaths in 12 U.S. Cities. *Environmental Health Perspectives* 2002; 110(9):859-869.
3. Braga AL, Zanobetti A, Schwartz J. The Time Course of Weather Related Deaths. *Epidemiology* 2001; 12:662-667.
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Theme II Project IIb: Assessing Life-Shortening Associated with Exposure to Particulate Matter

Investigators:

T. Bateson, B. Coull, M. O'Neill, J. Schwartz, A. Zanobetti

Institution:

Harvard School of Public Health

Description and Objectives of Research:

During the first two years of the PM Center grant this project dealt primarily with harvesting. For subsequent years, the primary focus was on the development of statistical methods for investigating confounding, dose-response relationships and other particle health effects issues. The main objective of the harvesting research effort was to examine whether particles advance mortality by a few days (harvesting) or have a more profound impact on public health. Another key issue in assessing the life-shortening effects of PM exposure is the question of dose-response. If there are thresholds for the effects of particles on deaths or hospital admissions then estimates of the public health effect will be overstated. To date, PM health effects studies suggest a no-threshold dose-response relationship. If in fact there are thresholds for the effects of particles on deaths or hospital admissions exist, however, estimated health effects may be overstated.

Summary of Findings/Accomplishments:

Harvesting. We published several papers on harvesting. The first two used a smoothing approach to examine the association of PM over time with daily deaths in Boston (Schwartz 2000c) and Chicago (Schwartz 2001). Hospital admissions were also examined in the second paper. The main conclusions of those analyses were that particle effects on mortality and morbidity become stronger as average time increases, thus rejecting the harvesting hypothesis. We continued analyses investigating harvesting in 10 European cities by examining all cause, respiratory, and cardiovascular deaths, for all ages and stratifying by age groups. Our study confirmed that most of the effect of air pollution is not simply advanced by a few weeks and that effects persist for over a month after exposure. We found that the effect size estimate for PM₁₀ doubles when we considered longer term effects for all mortality and cardiovascular mortality and becomes five times higher for respiratory mortality. We found similar effects when stratifying by age groups (Zanobetti et al. 2003). In a related matter, we also clarified that control for influenza and other respiratory epidemics does not change the effect size estimates for PM effects on daily deaths (Braga et al. 2000).

Dose-Response. We developed a new methodology that allows combining smoothed dose-response curves from multiple locations and demonstrated its effectiveness using simulation studies to examine this result. Subsequently, we applied this method to analyze daily deaths in 10 US cities. No deviation from linearity down to the lowest exposure concentrations was observed (Schwartz 2000a). In addition, case-crossover studies were developed and applied to examine the association between PM_{2.5} concentrations and hospital admissions for myocardial infarctions (MIs) in Boston (Zanobetti and Schwartz 2006).

We extended this methodology to incorporate heterogeneity in response across cities by developing a smoothed estimate that allows heterogeneity to vary by exposure level. This new methodology was then applied to eight cities in Spain (Schwartz et al. 2001). We also applied this methodology to two-pollutant models and examined the sensitivity of the dose-response curve shape to the way season and weather were controlled. We found a significant linear association between daily deaths and black smoke. This association was little changed by variations in control for weather, season or SO₂. For SO₂, the association was implausible (inverted U shape) and disappeared after controlling for black smoke (Sunyer et al. 2003). Finally, we have used hierarchical models to identify predictors of heterogeneity in nonlinear dose-response curves. This method was applied to examine the dose-response relationship between PM₁₀ and hospital admissions for heart and lung disease. A manuscript is under preparation but has not been submitted for review.

Co-pollutants. Additionally, we made important progress in assessing the effects of confounding by co-pollutants on the relation between particles and morbidity and mortality. We investigated the confounding effect of gaseous co-pollutants for both morbidity and mortality. We developed a hierarchical model to assess confounding and applied it to examine the association between PM₁₀ and daily deaths (Schwartz 2000b). The results of this analysis suggested that associations were not confounded by gaseous air pollutants. Further work has shown that the two-stage hierarchical modeling approach is more resistant to measurement error in the pollutants and confirmed that there is no association of gaseous co-pollutants with mortality in ten US cities (Schwartz and Coull 2003).

Timing of the effect. We found that the PM₁₀ effects on myocardial infarction deaths occur on the same day, while for other cardiovascular deaths the lag is about a day. For respiratory deaths one- and two-day lags were observed. These patterns can be explained physiologically and can help to elucidate biological mechanisms (Braga et al. 2001).

Statistical methods. Finally, we demonstrated that it is possible to control for season and analyze mortality and morbidity using the case crossover approach (Bateson and Schwartz 1999). We showed that there could be a selection bias and that it can be estimated and corrected (Bateson and Schwartz 2001). Using this approach, we investigated the association between PM₁₀ and daily deaths in Cook County, Illinois (Bateson and Schwartz 2004).

After the first few years of the Center, the validity of using generalized additive models to assess PM health outcomes was under examination. Center investigators spent a great deal of time addressing this issue. Towards this end, we re-analyzed our 10-city mortality study, the Six City time series study, the Six City Source Apportionment Study, our hospital admissions studies and

the long term distributed lag models from the APHEA study. Additional work showed that then current approaches misestimated the standard errors of parametric terms when controlling for smooth functions. This raised questions about the entire approach. In addition to re-analyzing the data using different convergence criteria and natural splines, we developed alternative approaches including the penalized spline method (Schwartz et al. 2002). The results of the re-analysis did not change substantially from previously reported results. (Schwartz et al. 2002).

Conclusions:

Through this work, we found that particle effects on mortality and morbidity become stronger as average time increases, thus rejecting the harvesting hypothesis. We also confirmed that most of the effect of air pollution is not simply advanced by a few weeks and that effects persist for more than a month after exposure. We also clarified that control for influenza and other respiratory epidemics does not change the effect size estimates for PM effects on daily deaths.

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Theme II Project IIc: Investigating Chronic Effects of Exposure to Particulate Matter

Investigators:

D. Dockery, F. Laden, J. Schwartz

Institution:

Harvard School of Public Health

Description and Objectives of Research:

We followed up the Six Cities Study cohort in an effort to assess the cumulative effect of long-term exposures on the incidence of lung cancer, nonmalignant respiratory disease, cardiovascular disease, and cause-specific mortality. Vital statistics were determined for the 8,111 participants in the Harvard Six Cities adult cohort for an additional nine years of follow-up (1990-1998). We identified 1,430 additional deaths bringing the total to 2,737 deaths.

Summary of Findings/Accomplishments:

During the follow-up period, 1990-1998, air pollution levels decreased in two of the cities, while they remained about the same in the other four. Monitoring of PM_{2.5} and PM₁₀ was included as part of the original study, but it was not continued in the more recent period of follow-up. Therefore, we modeled PM_{2.5} for this time period using data from nearby monitors in the EPA Air Quality System monitoring network. Accordingly, a paper showing a decrease in the relative risk from mortality consistent with decreased air pollution levels in specific cities was published (Laden et al. 2006). We found an increase in overall mortality associated with each 10 µg/m³ increase in PM_{2.5} modeled either as the overall mean (rate ratio [RR], 1.16; 95% confidence interval [CI], 1.07-1.26) or as exposure in the year of death (IRR, 1.14; 95% CI, 1.06-1.22). PM_{2.5} exposure was associated with lung cancer (1111, 1.27; 95% CI, 0.96-1.69) and cardiovascular deaths (RR, 1.28; 95% CI, 1.13-1.44). Improved overall mortality was associated with decreased mean PM_{2.5} (10 µg/m³) between periods (RR, 0.73; 95% CI, 0.57-0.95). Survival analyses of all-cause mortality shows that life expectancy continues to be reduced in the more polluted cities, with the survival relative ranking being the same as that observed in the original study.

In addition, we completed an analysis of the effects of control of particulate air pollution on mortality in Dublin, Ireland (Clancy et al. 2002). Because of high particulate (Black Smoke) levels, the Irish government banned the sale of coal within the city of Dublin as of September 1990. We showed that mean black smoke concentrations dropped by 36 µg/m³ following the ban. After adjusting for the age distribution of the population, weather, influenza epidemics, and

background mortality in the rest of Ireland, Dublin total mortality rates dropped by 6%, respiratory mortality dropped by 16%, and cardiovascular mortality by 10%.

Additional analysis using distributed lag models found the effects of both particulate air pollution and temperature on mortality persisted for 3–4 weeks after exposure (Goodman et al. 2004). The temperature effects were more prolonged for respiratory deaths compared to cardiovascular deaths. The effects of particulate air pollution on mortality were strongest on the day of and the few days after exposure but extend out through about 40 days after exposure. This extended air pollution association was most marked for the elderly population groups and for respiratory causes of death. These extended follow-up effects were two to three times greater than the acute effects reported in other studies and approach the effects reported in longer-term survival studies.

Conclusions:

The follow-up analysis of the Six Cities Study found total, cardiovascular, and lung cancer mortality to be positively associated with ambient PM_{2.5} concentrations. Reduced PM_{2.5} concentrations were associated with reduced mortality risk.

Similarly, markedly reduced black smoke and particulate levels in Dublin, due to a ban on coal sales in the city, were associated with reduced mortality from respiratory and cardiovascular causes. Further analysis suggested that the studies on the acute effects of air pollution have underestimated the total effects of temperature and particulate air pollution on mortality.

Publications:

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Theme II Project IId: Determining the Effects of Particle Characteristics on Respiratory Health of Children

Investigators:

D. Dockery, H. Luttmann-Gibson

Institution:

Harvard School of Public Health

Description and Objectives of Research:

The main objective of this project was to examine the effects of particle composition on the respiratory health of children using PM samples collected as part of the Harvard 24-Cities study.

Summary of Findings/Accomplishments:

The Harvard 24-Cities Study assessed respiratory health and particle exposures of 13,364 fourth and fifth grade school children in the United States and Canada between 1988 and 1991. The University of Southern California Children's Health Study had similarly assessed respiratory health and particle exposures of approximately 4000 fourth and fifth grade school children in twelve communities in Southern California. The Harvard study was designed to assess effects of power plant particles, while the Southern California Study focuses on effects from mobile source particles. The Harvard Study included one Southern California community (Simi Valley) and two other California sites (Monterey and Livermore).

The chemical analysis and data processing of the 24-Cities samples was completed. The statistical analysis of the exposure and health data was initiated, but it was not completed. Preliminary results of this analysis presented in the 2003 SAC meeting, showed no association between air pollution-caused respiratory effects and elemental carbon concentrations. We planned to conduct a collaborative inter-center assessment of the effects of chronic particulate exposures on respiratory health of children. We expected that pooling these studies will greatly improve our ability to assess the relative contribution of power plant versus mobile source particles on respiratory health of children. These additional analyses have not been completed.

Conclusions:

N/A.

Publications:

N/A.

THEME III: BIOLOGICAL MECHANISMS/DOSIMETRY

Theme III focused upon mechanisms of cardiac vulnerability as a result of air pollution exposure. Many of our CAPs animal toxicology and human panel studies have linked pulmonary and cardiovascular health outcomes to different PM components such as trace metals, elemental carbon, sulfates and silicon (Batalha et al. 2002, Clarke et al. 2000, Saldiva et al. 2002). Reanalysis of the Harvard Six Cities study provided strong evidence of increased toxicity associated with combustion-related PM from traffic and power plants compared to soil dust (Laden et al. 2000).

The objectives of Theme III were to identify the particulate and gaseous air pollutants responsible for increased cardiac vulnerability as an adverse health effect and to define the biological mechanisms that lead to this outcome. As part of this theme, we specifically worked to: (1) identify the physical and chemical properties of particulate matter responsible for the observed adverse health effects; (2) determine whether gaseous co-pollutants exacerbate the effects of particles; (3) investigate the biological mechanisms by which particulate matter produces mortality and acute or chronic morbidity; and (4) examine particle deposition patterns and fate in the respiratory tract. These objectives were addressed in several areas of research that explored the components of air pollution that cause adverse health effects and the biological mechanisms that may lead to fatal outcomes. The projects under this theme built upon the findings from a number of our previous animal studies, which made it possible to explore and define both cardiac and pulmonary responses to inhaled fly ash and concentrated ambient particles (Killingsworth et al. 1997).

Theme III Project IIIa: Identifying the physical and chemical properties of particulate matter responsible for the observed adverse health effects

Investigators:

J. Godleski, B. Coull, J. Lawrence, P. Koutrakis,

Institution:

Harvard School of Public Health

Description and Objectives of Research:

Although many of the individual toxicological studies described here were done with support of other grants, the final analyses were done with support from our EPA Center. The primary objectives of the analyses conducted for this project were: to characterize the components of CAPs that are significantly associated with the development of pulmonary inflammation; to determine whether short term exposures to CAPs alter the morphology of small pulmonary arteries; and to determine if increased pathologic responses may have similarly resulted from concentrated exposures to what may be considered non-toxic silicate particles. These analyses have resulted in a number of publications, several of which are described below (Batalha et al. 2002, Saldiva et al. 2002, Godleski et al. 2002).

To characterize the components of CAPs that are significantly associated with the development of pulmonary inflammation, mature male rats were exposed to CAPs using the Harvard/EPA Ambient Particle Concentrator (HAPC) to determine if pulmonary inflammation was affected in a dose-dependent manner. Chronic bronchitic (CB) rat were employed as a model of pulmonary disease (250 ppm SO₂ x 5 days/week for 6 weeks). Age-matched, room air-exposed rats were used as a normal control group. For urban particle exposures, normal or CB animals were exposed by inhalation for 6 hours/day for three consecutive days to CAPs or filtered air. In all, we had six complete studies as outlined in Table 1 below. This number of experimental exposures allowed us to relate CAPs composition to animal responses. Before the first day of exposure, and after the last day of exposure, animals in each group had breathing pattern studies using the BUXCO analysis system. On the day after the last exposure, animals were sacrificed and studied by bronchoalveolar lavage (BAL), collection of BAL cellular RNA, total lung RNA and collection of lung and heart tissues for morphologic studies.

Table 2. Experimental Design

Date	Total # of Animals	Number of animals for BAL Studies				No. of Animals for Histology Studies	No. of Animals for BUXCO Studies	Three-Day Mean CAPs ($\mu\text{g}/\text{m}^3$)	Conc. Factor
		Air		CB					
		Sham	CAPs	Sham	Caps				
Mar. 1997	40	8	8	8	8	2	none	170.7	19.9
June 1997	40	8	8	8	8	2	6-8	481.0	29.9
Sept 1997	48	10	10	10	10	2	15-21	187.1	12.1
Jan 1998	47	8	8	8	8	3-4	9-12	126.1	18.2
Mar. 1998	40	8	8	7	8	2-3	6-12	267.3	35.1
June 1998	44	7	8	8	8	2-4	8-12	300.7	38.2

Summary of Findings/Accomplishments:

In the assessment of pulmonary inflammation, bronchoalveolar lavage (BAL) was conducted on the animals. The numerical density of neutrophils (Nn) in two areas of the alveolar walls was assessed. CAPs and several PM components induced a significant increase in BAL neutrophils in normal animals. Among components, lead (Pb) had the most significant association. No other cell type had any significant change. In rats with chronic bronchitis, significant increases in BAL neutrophils were associated with all components except chlorine (representing sea salt aerosols). In addition, in bronchitic rats, lymphocytes were also significantly increased in association with vanadium ($p < 0.01$) as well as traffic related factors Br, Pb, EC and organic carbon (OC) ($p < 0.05$). Of BAL fluid components, Pb, SO_4^{2-} , EC, OC and Si were associated with increases in protein. Greater Nn was observed in the central compared to peripheral regions of the lung. When responses were assessed in relationship to component concentrations in the exposures, robust, significant, and dose-dependent associations between Nn and the concentrations of V, Br, Pb, EC and OC were found. Thus, short-term exposures of rats to CAPs from Boston induce a significant inflammatory reaction in the lungs dependent upon the concentration of airborne components. Results of the BAL studies show that significant increases in neutrophils were found in normal rats, and rats with chronic bronchitis had an enhanced response. Increases in lymphocytes and protein in BAL fluid were also observed in the chronic bronchitic animals. In the tissue studies, Nn was significantly increased in normal animals, but a significant change was not detected in the chronic bronchitic animals. Given the BAL results, it is likely that the difference may have been more difficult to detect morphologically with the presence of chronic bronchitis. Nevertheless it is clear that CAPs exposure increases pulmonary inflammation (Saldiva et al. 2002).

We also studied the pulmonary response to CAPs using normal animals from which we have collected total lung RNA (Godleski et al. 2002). The RNA was pooled, labeled, and hybridized to multiple Affymetrix rat micro-array chips (A-chips) to explore the range of responses to CAPs exposure. Using the A-chip results, data from the sham-exposed group was subtracted from the CAPs group. Since these chips typically include multiple measurements of the same gene, cluster analyses of the results as well as biologic responder cluster assessments of these micro-array studies strongly support the pro-inflammatory potential of CAPs. An overall increase in pro-inflammatory mediators such as C-C chemokines, IL-1, IL-6 and TNF is illustrated with an overall decrease in immune enhancers such as IL-2 and interferon.

To determine whether short term exposures to CAPs alter the morphology of small pulmonary arteries in normal rats and rats with CB, Sprague-Dawley male rats were exposed to CAPs using the Harvard Ambient Particle Concentrator (HAPC), or to particle-free air (sham) under identical conditions during three consecutive days (5h/day) in six experimental sets (Batalha et al. 2002). Histological slides were prepared from random sections of lung lobes and coded for blinded analysis. The lumen/wall area ratio (L/W) was determined morphometrically on transverse sections of small pulmonary arteries. When all animal data (normal and CB) were analyzed together, the L/W ratios decreased as concentrations of $\text{PM}_{2.5}$, Si, Pb, SO_4^{2-} , EC and OC increased. In separate univariate analyses of animal data, the association for sulfate was

significant only in normal rats, whereas silicon was significantly associated in both CB and normal rats. In multivariate analyses including all particle factors, the association with silicon remained significant. Our results indicate that short-term CAPs exposures (median 182.75, range 73.50-733.00 $\mu\text{g}/\text{m}^3$) can induce vasoconstriction of small pulmonary arteries in normal and CB rats. This effect was correlated with specific particle components, and suggests that the pulmonary vasculature might be an important target for ambient air particle toxicity

Since our group utilizes the HAPC to generate concentrated aerosols of outdoor air particles for experimental exposures, and since we have reported increased pathologic responses to inhalation of concentrated urban air particles and identified silicon (as silicate) as an element associated with many of these responses, we sought to determine whether the HAPC may have had some effect on what may be considered non-toxic silicate particles. Using silicate rich Mt. St. Helen's volcanic ash (MSHA), we exposed three groups of Sprague-Dawley rats by inhalation for 6 hours to filtered air, MSHA, or MSHA passed through the HAPC (Savage et al. 2003). Twenty-four hours following exposure, BAL was performed to assess total cell count, differential cell count, protein, lactate dehydrogenase, and n-beta glucosaminidase levels. Peripheral blood was examined for packed cell volume, total protein, total white cells, and differential cell count. Morphologic studies localized particles in the lung and assessed pulmonary vasculature. No significant differences were observed among any of the groups in any parameter measured including morphometric analysis of pulmonary vasoconstriction. Scanning electron microscopy and x-ray analysis identified particles as silicates typical of MSHA throughout the lung. Our findings suggest that particles passing through the HAPC have no change in their toxic potential in an exposure setting where particle deposition in the lung has occurred.

Conclusions:

Data from our animal studies suggest that short-term exposures to CAPs from Boston induce a significant inflammatory reaction in rat lungs, with this reaction influenced by particle composition. Our results also demonstrate that the short-term CAPs exposures can induce vasoconstriction of small pulmonary arteries in normal and CB rats. The magnitude of the observed vasoconstrictive response to CAPs exposure is related to CAPs mass and specific particle constituent concentrations. Thus, vasoconstriction of pulmonary vessels associated with CAPs exposures may be the result of an effect at the level of the pulmonary vascular endothelial cells with an abnormal balance between releasing of endothelium-derived constricting factors and endothelium-derived relaxing factors. We speculate that the resultant pulmonary endothelial dysfunction with predominant release of mediators that constrict vessels could lead to a dominant vasoconstrictive status in the lungs and possibly in the heart. There is also evidence in the microarray studies for increases in ROS activity, as well as evidence for activation of organic chemical metabolism and detoxification mechanisms.

Publications:

1. Batalha J, Saldiva H, Clarke R, Coull BA, Stearns R, Lawrence J, Murthy GGK, Koutrakis P, Godleski J. Concentrated Ambient Air Particles Induce Vasoconstriction of Small Pulmonary Arteries in Rats." *Environmental Health Perspectives* 2002; 110(12):1191-1197.
2. Clarke RW, Coull BA, Reinisch U, Catalano P, Killingsworth CR, Koutrakis P, Kavouras I, Murthy GGK, Lawrence J, Lovett E, Wolfson JM, Verrier RL, Godleski JJ. Inhaled Concentrated Ambient Particles are Associated with Hematologic and Bronchoalveolar Lavage Changes in Canines. *Environmental Health Perspectives*, 2000; 108(12):1179-87.
3. Godleski J, Clarke R, Coull B, Saldiva P, Jiang N, Lawrence J, Koutrakis P. (2002). "Composition of Inhaled Urban Air Particles Determines Acute Pulmonary Responses. *Annals of Occupational Hygiene Supplement 1* 2002; 46:419-424.
4. Hamada K, Goldsmith CA, Suzaki Y, Goldman A, Kobzik L. Airway Hyperresponsiveness Caused by Aerosol Exposure to Residual Oil Fly Ash Leachate in Mice. *Journal of Toxicology and Environmental Health A* 2002; 65(18):1351-65.
5. Saldiva PHN, Clarke RW, Coull BA, Stearns RC, Lawrence J, Murthy GGK, Diaz E, Koutrakis P, Suh HH, Tsuda A, Godleski JJ. Lung Inflammation Induced by Concentrated Ambient Air Particles is Related to Particle Composition." *American Journal of Respiratory and Critical Care Medicine* 2002; 165(12):1610-1617.
6. Savage, S., J. Lawrence, T. Katz, R. Stearns, B. Coull and J. Godleski (2003). "Does the Harvard/Environmental Protection Agency Ambient Particle Concentrator change the toxic potential of particles." *Journal of the Air and Waste Management Association* 53: 1088-1097.

Theme III Project IIIb: Differentiating the Roles of Particle Size, Particle Composition, and Gaseous Co-Pollutants on Cardiac Ischemia

Investigators:

J. Godleski, B. Gonzales-Flecha, G. Wellenius

Institution:

Harvard School of Public Health

Description and Objectives of Research:

To improve understanding of mechanisms, we developed and tested a model for investigating the effects of inhaled PM on arrhythmias and HRV, a measure of autonomic nervous system activity, in rats with acute MI (Wellenius et al. 2002). Left-ventricular MI was induced in Sprague-Dawley rats by thermocoagulation of the left coronary artery; additional rats served as sham-operated controls. Diazepam-sedated rats were exposed (1h) to either residual oil fly ash (ROFA), BC, or room air, 12-18 hours after surgery. Each exposure was immediately preceded and followed by a 1h exposure to room air (baseline and recovery periods, respectively). Lead II electrocardiograms were recorded. This rat model was also used in two additional studies, described below, evaluating effects of CAPs and CO on arrhythmias (Wellenius et al. 2004, Wellenius et al. 2006)

Summary of Findings/Accomplishments:

In the MI group, 41% of rats exhibited one or more premature ventricular complexes (PVCs) during the baseline period. Exposure to ROFA, but not to BC or room air, increased arrhythmia frequency in animals with pre-existing PVCs. Furthermore, MI rats exposed to ROFA, but not to carbon black or room air, decreased HRV. There was no difference in arrhythmia frequency or HRV among sham-operated animals (Wellenius et al. 2002).

As ambient air pollution is a complex mixture of PM and gaseous pollutants such as carbon monoxide (CO), the effect of exposure to CO, alone or in combination with ambient PM, on arrhythmia incidence in the MI model was studied (Wellenius et al. 2004). To evaluate the arrhythmogenic potential of ambient PM and CO, individually and together, left-ventricular myocardial infarction was induced in rats by thermocoagulation. Diazepam-sedated rats were exposed (1h) to either filtered air (n=43), CO (35 ppm, n=21), CAPs, mean concentration=523.1 µg/m³, n=58), or CAPs and CO (n=24), 12-18h after surgery. Each exposure was immediately preceded and followed by a 1h exposure to filtered air (baseline and recovery periods, respectively). The CO target dose of 35 ppm is related to the 1hr US National Ambient Air

Quality Standard. Lead II electrocardiograms were recorded and heart rate and arrhythmia incidence were quantified. CO exposure alone and with CAPs reduced VPCs frequency by 60.4% ($p=0.012$) during the exposure period as compared to the filtered air group. This effect was modified by both infarct type and the frequency of VPCs at baseline, and was not mediated through changes in heart rate. CAPs exposure had no effect on VPC frequency overall, but led to a reduction in VPCs during the recovery period in animals with a high number of baseline VPBs, relative to the controls. This effect was likely mediated by a CAPs dose-dependent increase in heart rate. No significant interactions were observed between the effects of CO and CAPs.

Since recent studies suggest an association between $PM_{2.5}$ and supraventricular arrhythmias (SVA), we evaluated this association in a rat model of acute MI. Diazepam-sedated Sprague-Dawley rats with MI (Wellenius et al. 2006). The animals were exposed for 1 h to either: (1) filtered air ($n=16$); (2) CAPs (mean= $645.7 \mu\text{g}/\text{m}^3$, $n=23$); (3) carbon monoxide (CO; 35 ppm; $n=19$); or (4) CAPs and CO ($n=24$). Each exposure was immediately preceded and followed by a 1 h exposure to filtered air (baseline and post-exposure periods, respectively). Surface electrocardiograms were recorded and the frequency of supraventricular premature beats was quantified. Among rats in the CAPS group, the probability of observing any SVA decreased from baseline to the exposure and post-exposure periods. This pattern was significantly different than that observed for the filtered air group during the exposure period ($p=0.048$) only. In the subset of rats with one or more SVA during the baseline period, the change in SVA rate from baseline to exposure period was significantly lower in the CAPs ($p=0.04$) and CO ($p=0.007$) groups only, as compared to the filtered air group. No significant effects were observed in the group simultaneously exposed to CAPs and CO. The results of this study do not support the hypothesis that exposure to ambient air pollution increases the risk or frequency of supraventricular arrhythmias.

Conclusions:

These results underscore the usefulness of this model for elucidating the physiologic mechanisms of pollution-induced cardiovascular arrhythmias and contribute to defining the specific constituents of ambient particles responsible for arrhythmias. Inhalation of combustion-derived PM clearly exacerbates cardiac vulnerability following acute MI.

Publications:

1. Wellenius, G., B. Coull, J. Batalha, E. Diaz, J. Lawrence and J. Godleski (2006). "Effects of ambient particles and carbon monoxide on supraventricular arrhythmias in a rat model of myocardial infarction." *Inhalation Toxicology* 18: 1077-1082.
2. Wellenius, G., J. Batalha, E. Diaz, J. Lawrence, B. Coull, T. Katz, R. Verrier and J. Godleski (2004). "Cardiac effects of carbon monoxide and ambient particles in a rat model of myocardial infarction." *Toxicological Sciences* 80: 367–376.

3. Wellenius, G., B. Coull, J. Godleski, P. Koutrakis, K. Okabe, S. Savage, J. Lawrence, G. G. K. Murthy and R. Verrier (2003). "Inhalation of concentrated ambient air particles exacerbates myocardial ischemia in conscious dogs,." Environ Health Perspect 111(4): 402-408.
4. Wellenius, G., P. Saldiva, J. Batalha, G. G. K. Murthy, B. Coull, R. Verrier and J. Godleski (2002). "Electrocardiographic changes during exposure to residual oil fly ash (ROFA) particles in a rat model of myocardial infarction." Toxicological Sciences 66: 327-335.

Theme III Project IIIc: Toxicological Evaluation of Realistic Emissions of Source Aerosols (TERESA) Study

Investigators:

P. Koutrakis, J. Lawrence, P. Ruiz, M. Wolfson

Institution:

Harvard School of Public Health

Description and Objectives of Research:

The TERESA study is a large scale project requiring extensive method development. This research was initiated under the Center with additional funding provided by the Electric Power Research Institute and the US Department of Energy. The primary goal of TERESA is to evaluate the comparative toxicity of secondary particles derived from coal-fired power plant emissions and vehicular sources. Three power plants were included in the project to allow assessment of different coals and pollution control configurations. Toxicological tests have been completed for two of the three plants and are currently underway at the third. Future work will include toxicological tests of both primary and secondary vehicle emissions.

Primary emissions were drawn from the power plant stacks into a mobile reaction laboratory, where several atmospheric scenarios were simulated: 1) primary particles only; 2) oxidized emissions; 3) oxidized emissions + secondary organic aerosol (SOA), and; 4) oxidized emissions + ammonia + SOA. The study design included a two-stage toxicological assessment. In Stage I, overall cardiac and pulmonary toxicity was to be determined in normal laboratory rats, followed by a more comprehensive and cardiac-focused Stage II assessment in a compromised rat model. Because no adverse biological effects were observed in Stage I for the first power plant, the Stage II assessment was only conducted at the second plant.

Sampling and Exposure Methods. The emissions sampling system is described in detail in a manuscript currently in preparation (Ruiz et al. 2006a). The design of the emissions sampling system represented a technical challenge, with significant care being taken to minimize particle losses in the system. A continuous sample passes from a pre-stack duct to a mobile chemical laboratory on the ground. Controls are used to adjust temperature and particle concentrations. The air is then passed to the atmospheric reaction simulation system. The atmospheric reaction simulation system is described in detail in a manuscript recently submitted for publication (Ruiz et al. 2006c). This dual-chamber conceptual model includes ultraviolet light to allow for oxidation of SO₂ followed by introduction of ammonia to produce acidic sulfate particles. Excess reactive gases are removed from the first stage reaction mixture (while keeping the secondary particles suspended in air) using denuders. The denuder system is described in detail in Ruiz et al. 2006b.

In field monitoring, analytical measurement of the exposure atmospheres was extensive, to monitor and document performance of the two reaction chambers and to characterize the exposure atmospheres. For exposure characterization, continuous measurements included PM_{2.5} mass, particle number, SO₂, NO_x, O₃, temperature and; relative humidity. Integrated measurements included PM_{2.5} mass, particle sulfate, particle nitrate, particle strong acidity, particle ammonium, particle elements, EC, OC, SO₂, nitric acid vapor, nitrous acid vapor, ammonia, ketones, aldehydes and α -pinene.

Toxicological Methods. Animal exposures were performed using both normal and compromised female Sprague-Dawley rats in a separate mobile animal exposure laboratory. In the mobile reaction laboratory, photochemically aged air was diluted with humidity-controlled clean air (ambient air with pollutant gases and particles removed) and transmitted to the exposure laboratory. In the exposure laboratory, air was drawn through individual exposure chambers in parallel. Exposures were six hours in duration and were immediately preceded and followed by a one-hour exposure to humidity adjusted zero air (baseline and recovery periods, respectively). Each scenario included four days of exposures, each with five rats (two for *in vivo* oxidative stress and three for the other biological endpoints). Pulmonary, cardiac, and systemic effects were evaluated via BAL, histopathology, pulmonary function, *in vivo* oxidative stress and blood cytology. At autopsy, total lung volumes were determined, and the lungs were cut horizontally into 2 mm numbered sections. Three sections were randomly selected for processing by paraffin histology techniques. *In vivo* oxidative stress was measured using organ chemiluminescence.

Summary of Findings/Accomplishments:

Toxicological Effects. The results of the data analysis for the first two power plants of the TERESA study is summarized as follows: a) the results from the analysis of the lung and cardiac histology BAL and blood data were negative (no effects found for either plant); b) there was evidence for respiratory breathing pattern effects, which were associated with sulfates and mass at the second plant and when both plants were combined, but not at the first plant alone; c) no chemiluminescence effects were found at the first plant; d) these effects were found for both heart and lung at the second plant; e) the data show tissue specific associations for the CL effects, with OC and mass being important contributors to the responses in the heart, and metals and non-sulfate mass more important to the responses in the lung. Results from the proposed organic carbon-only exposures at power plant 3 will help us to interpret these results. The rats with the myocardial infarction model, had an 87% increase in premature ventricular beats which was statistically significant. Papers describing these results in detail are in preparation.

Conclusions:

As the results from the toxicological studies are preliminary, conclusions regarding primary exposure scenarios cannot be provided.

Publications:

1. Ruiz, P., J. Lawrence, S. Ferguson, J. Wolfson and P. Koutrakis (2006). "A counter-current parallel-plate membrane denuder for the non-specific removal of trace gases." *Environmental Science & Technology* 40(16): 5058-5063.

Theme III Project IIId: Assessing Deposition of Ambient Particles in the Lung

Investigators:

J. Godleski, A. Tsuda

Institution:

Harvard School of Public Health

Description and Objectives of Research:

Center activities focused on the development of theoretical models to predict PM deposition as a function of particle size (Tsuda et al. 2002; Henry et al. 2002; Haber et al. 2003). Subsequently, a series of human ambient particle deposition studies were conducted (Montoya et al. 2004).

Summary of Findings/Accomplishments:

In Tsuda et al. 2002, we demonstrated, through flow visualization studies in rhythmically ventilated rat lungs, that chaotic mixing may be key to aerosol transport in the lungs. We found substantial alveolar flow irreversibility with stretched and folded fractal patterns, which led to a sudden increase in mixing. These findings support the theory that chaotic alveolar flow governs gas kinematics in the lung periphery, and hence the transport, mixing, and ultimately the deposition of fine aerosols.

In Henry et al. 2002, we described the behavior of fluid particles (or bolus) in a realistic, numerical, alveolated duct model with rhythmically expanding walls. We found acinar flow exhibiting multiple saddle points, characteristic of chaotic flow, resulting in substantial flow irreversibility. Computations of axial variance of bolus spreading indicated that the growth of the variance with respect to time is faster than linear, a finding inconsistent with dispersion theory. Lateral behavior of the bolus shows fine-scale, stretch-and-fold striations, exhibiting fractal-like patterns with a fractal dimension of 1.2, which compares well with the fractal dimension of 1.1 observed in our experimental studies performed with rat lungs. We concluded that kinematic irreversibility of acinar flow due to chaotic flow may be the dominant mechanism of aerosol transport deep in the lungs.

In Haber et al. 2003 we tested the hypothesis that the trajectories and deposition of aerosols inside the alveoli differ substantially from those previously predicted. To test this hypothesis, trajectories of fine particles (0.5 - 2.5 μm in diameter) moving in the foregoing alveolar flow field and simultaneously subjected to the gravity field were simulated. The results show that alveolar wall motion is crucial in determining the enhancement of aerosol deposition inside the

alveoli. In particular, 0.5- to 1- μm -diameter particles are sensitive to the detailed alveolar flow structure (e.g., recirculating flow), as they undergo gravity-induced convective mixing and deposition. Accordingly, deposition concentrations within each alveolus are nonuniform, with preferentially higher densities near the alveolar entrance ring, consistent with physiological observations. Deposition patterns along the acinar tree are also nonuniform, with higher deposition in the first half of the acinar generations. This is a result of the combined effects of enhanced alveolar deposition in the proximal region of the acinus due to alveoli expansion and contraction and reduction in the number of particles remaining in the gas phase down the acinar tree. We concluded that the cyclically expanding and contracting motion of alveoli plays an important role in determining gravitational deposition in the pulmonary acinus.

In addition, we conducted a series of exposure experiments to test the hypothesis that the lung deposition of ambient particles (i.e., CAPs) can not be adequately described based on findings with conventionally used 'test particles' such as iron oxide particles because of the complex physicochemical properties of CAPs. In the course of eight experiments performed so far, dogs were exposed to CAPs and control particles (iron oxide, mean diameter of 0.7 μm) and the total deposition of these particles was computed and compared over a wide range of particle size (40 nm - 3 μm). The initial results showed that: (1) changes in relative humidity along the airways influenced CAPs characteristics and consequently their behavior in the respiratory tract; and (2) the total deposition of CAPs was substantially higher than that of control particles. These results suggest that the hygroscopic properties of CAPs may be important in determining deposition, and that the estimation based on nonhygroscopic control particles could substantially underestimate the particle deposition for a given exposure.

The total deposition fraction of fine and ultrafine aerosols was measured in a group of six healthy adults exposed to Boston ambient particles. During these exposures particle mass and number concentration ranged from 7 and 32 $\mu\text{g}/\text{m}^3$ and from 16,100 and 64,100 $\#/\text{cm}^3$, respectively. Fifteen repeated inhalation-exhalation cycles were conducted during a given exposure session. The deposition efficiency of particles ranging from 40 to 2045 nm was determined using the average concentration of inhaled and exhaled particles measured during these cycles. Deposition efficiencies ranged between $7.3 \pm 18.7\%$ (for particles 168 - 195 nm) and $98.6 \pm 28.1\%$ (for particles 1545 - 2045 nm). Subjects exhibited similar deposition patterns with a minimum efficiency in the size range of 100 - 200 nm. Results from analysis of variance and mixed model regressions, suggested that deposition efficiency varied with individual and particle size. Deposition efficiencies varied mostly among subjects for particles in the size range between 100 and 1000 nm. Measured deposition efficiencies were compared to those reported by the International Commission on Radiological Protection (ICRP) model. For this comparison, the ICRP deposition efficiencies for a sitting female subject were used. The minimum deposition estimated by the model was at 400 - 500 nm, while our results show a minimum at about 100 nm. The ICRP model deposition efficiencies were lower for particles <150 nm, about 20%, and higher for particles >676 nm by about 20%. Inter-subject variability in airway morphology, differences in breathing patterns used in the model and, particle composition may account for the observed differences. This work was published in Montoya et al. 2004.

Conclusions:

Although acinar flow patterns likely have little effect on the gas exchange processes of highly diffusible respiratory gases (O₂ and CO₂), they play an important role in determining the fate of inhaled fine particles with low diffusivity and little gravitational sedimentation. We conclude that chaotic acinar flow may be the origin of substantial mixing and transport of fine aerosols deep in the lung.

Publications:

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2. Henry FS, Butler JP, Tsuda A. Kinematically Irreversible Acinar Flow: A Departure from Classical Dispersive Aerosol Transport Theories. *Journal of Applied Physiology* 2002; 92:835-845.
3. Montoya, L., J. Lawrence, G. G. K. Murthy, J. Sarnat, J. Godleski and P. Koutrakis (2004). "Continuous measurements of ambient particle deposition in human subjects." *Aerosol Science and Technology* 38: 980-990.
4. Tsuda A, Rogers RA, Hydon PE, Butler JP. Chaotic Mixing Deep in the Lung. *Proceedings of the National Academy of Sciences of the United States of America* 2002; 99(15):10173-10178.

Theme III Project IIIe: Relating Changes in Blood Viscosity, Other Clotting Parameters, Heart Rate and Heart Rate Variability to Particulate and Criteria Gas Exposures

Investigators:

S. Park, F. Speizer, F. Speizer

Institution:

Harvard School of Public Health

Description and Objectives of Research:

For another major project under Theme III of the Center, we monitored the health of approximately 700 Normative Aging Study (NAS) participants, who were examined between 2000 and 2003. The NAS is a longitudinal study of aging in Eastern Massachusetts established in 1963 by the Veterans Administration (VA). Community-dwelling men from the greater Boston metropolitan area were screened at entry and accepted into the study if they had no history of heart disease, hypertension, diabetes mellitus, cancer, peptic ulcer, gout, recurrent asthma, bronchitis, or sinusitis. Between 1963 and 1968, a total of 2,280 men were enrolled, ranging in age from 21 to 80 years (mean = 42 years) at entry. As of April 2004, 757 (mean age = 76±7 years) of the 2,280 men continue to participate in the study. 17% of these men are diabetic; 24% have coronary heart disease; 22% have COPD; and 58% are hypertensive. Correspondingly, beta-blockers are used by 33% of the subjects and calcium channel blockers by 14%; and 45% of the men are *GSTM1* null.

As part of the original NAS study, physical examinations of each study participant occur every three years at the Boston VA Hospital. At each of these visits, extensive physical examination, laboratory, anthropometric, and questionnaire data are collected, including height and weight, a complete medical history, and sitting heart rate, and dietary intake using the Willet semi-quantitative Food Frequency Questionnaire. In addition, sitting systolic (SBP) and diastolic blood pressures (DBP) are measured as the means of the left and right arm measurements. Blood samples are collected and analyzed for total serum cholesterol, high-density lipoprotein cholesterol, fasting blood glucose (FBG) levels, white cell counts with differentials, and other standard parameters. Information about cigarette smoking, alcohol consumption, medical history (including respiratory and cardiac symptoms), and medication use are obtained by self-administered questionnaire. Each subject is interviewed by a physician to confirm the identity and purpose of medications used. Incidence of new disease is also noted. For all reported coronary diseases, hospital records are obtained and reviewed by a board certified cardiologist. Criteria used to confirm coronary diseases follow the established protocols used in the Framingham Heart Study and are classified using the 10th edition of the International Classification of Disease. Subjects are recorded as having diabetes if they meet American

Diabetes Association criteria (FBG levels greater than 126 mg/dL and/or physician-diagnosed diabetes).

In addition to the regularly collected data, we collected additional electrocardiograph (ECG) measurements for each NAS participant at his/her clinic visit. Also, we analyzed collected blood samples for CRP, a marker of systemic inflammation. ECG recordings were analyzed for HRV. HRV measures included the standard deviation of NN intervals (SDNN), the square root of the mean of the squared differences between adjacent NN intervals (r-MSSD), total power (TP) (< 0.4 Hz), high frequency (HF) (0.15 to 0.4 Hz), low frequency (LF) (0.04 to 0.15 Hz), and LF/HF ratio using software complying with European Society of Cardiology and North American Society of Pacing and Electrophysiology guidelines. Subjects with atrial fibrillation, atrial bigeminy and trigeminy, pacemakers, irregular rhythm, irregular sinus rhythm, frequent ventricular ectopic activity, ventricular bigeminy, multifocal atrial tachycardia, or measurement time less than 3.5 minutes were not included in the analysis.

Summary of Findings/Accomplishments:

In this study, we found an association between reduced HRV and both PM_{2.5} and ozone, after controlling for age, diastolic blood pressure, fasting blood glucose level, cigarette smoking, angiotensin converting enzyme (ACE) inhibitor use, room temperature, season, and outdoor temperature (Park et al. 2005). Associations with BC were slightly weaker than those for PM_{2.5}, while other pollutants showed little association with HRV. The pollution associations were strongest for participants with hypertension (defined as either taking hypertension medication or having an SBP >140 or DBP > 90). The effects of PM_{2.5} and ozone on LF were muted or blocked in those taking either calcium channel blockers or β -blockers, while the HF response was not affected. Effect modification was not observed for participants on ACE inhibitors, which reduce blood pressure via different cardiac pathways.

Air pollution, HRV, and Genes related to Oxidative Stress. We have reanalyzed the association between air pollution and HRV using a subset of NAS participants for whom genotyping was performed as part of a separate study. In the subset analysis, no effect of particles was seen in subjects with *GSTM1* present, and a substantially greater effect was seen in those with the *GSTM1* deletion. In addition, three-way interactions were also seen, whereby the effect of PM was modified by both *GSTM1* and either obesity or elevated neutrophils (suggesting a role for systemic inflammation), or statins (which in addition to lowering cholesterol and CRP, have antioxidant properties, specifically enhanced NO synthase and reduced endothelin-1). Table 2 shows these results.

Table 2. Effect of 10 $\mu\text{g}/\text{m}^3$ $\text{PM}_{2.5}$ on HF by *GSTMI* status and other modifier

Category	N	% Change	95% CI
<i>GSTMI</i> Null, No Statin	162	-34.0	-53.0, -7.20
<i>GSTMI</i> Null, Statin	81	-6.4	-66.5, 161.9
<i>GSTMI</i> Present, No Statin	117	-3.6	-40.5, 56.2
<i>GSTMI</i> Present, Statin	81	-3.2	-50.0, 87.2
<i>GSTMI</i> Null, High Neutrophils*	64	-55.7	-88.0, 63.1
<i>GSTMI</i> Null, Normal Neutrophils‡	179	-36.1	-55.2, -8.7
<i>GSTMI</i> Present, High Neutrophils*	51	-49.6	-86.4, 86.1
<i>GSTMI</i> Present, Normal Neutrophils‡	147	17.6	-20.0, 73.0
<i>GSTMI</i> Null, Obese ^o	61	-57.3	-88.0, 52.0
<i>GSTMI</i> Null, not Obese ^o	182	-31.0	-50.6, -3.6
<i>GSTMI</i> Present, Obese ^o	54	-34.2	-77.9, 96.5
<i>GSTMI</i> Present, not Obese ^o	144	7.5	-29.7, 64.3

* Upper 25th percentile of the distribution in the study population

‡ Lower 75 percent of the distribution in the study population

^o Obesity – Body Mass Index (BMI) of 30 (kg/m^2) or greater

Air pollution, HRV, and genes related to metal metabolism. We also examined whether *HFE* modified the association between $\text{PM}_{2.5}$ and HRV in the NAS (Park et al. 2006). We found a 32.4% (95% confidence interval, 11.1% to 48.5%) decrease in high frequency (HF) component of HRV in persons with wild-type, whereas no relationship was observed in persons with either *HFE* variant. The difference in effect of $\text{PM}_{2.5}$ on HF between persons with and without *HFE* variants was significant (p for interaction = 0.02). We also found an association with LF, but only in the *HFE* variant carriers (19% reduction).

Ambient Pollution and Blood Markers of Inflammation/Endothelial Function. We examined the effects of several pollutants (BC, total particle count, and $\text{PM}_{2.5}$) on inflammatory markers and blood parameters for the 710 NAS subjects between 2000 and 2003. Fibrinogen was elevated in association with BC and particle count concentrations, and CRP was marginally significantly elevated in association with those particle measures in the entire cohort, and significantly elevated in association with particles in the subset with BMI over 30. A paper with these results is in press.

Conclusions:

Results from this study suggest that short-term exposures to $\text{PM}_{2.5}$ and O_3 are predictors of alterations in cardiac autonomic function as measured by HRV among older adults. Persons with IHD, hypertension, and diabetes appear to be more susceptible to autonomic dysfunction related to $\text{PM}_{2.5}$ exposure. The consistency of the effect modification observed in this and other studies strengthens the evidence that these conditions mark susceptibility to air pollution exposure and provides new information to guide research on underlying biological mechanisms.

Publications:

1. Baccarelli A, Zanobetti A, Martinelli I, Grillo P, Hou L, Giacomini SB, M., Lanzani G, Mannucci PM, Bertazzi PA, Schwartz J. Effects of Exposure to Air Pollution on Blood Coagulation. *Journal of Thrombosis and Haemostasis* 2007; doi:10.1111/j.1538-7836.2006.02300.x.
2. Baccarelli, A Zanobetti, A Martinelli, I Grillo, P Hou, L Giacomini, S Bonzini, M Lanzani, G Mannucci, P Bertazzi, P Schwartz, J, Effects of Exposure to Air Pollution on Blood Coagulation. *Journal of Thrombosis and Haemostasis*, 2007. 5, 2, 252–260.
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Theme III Project IIIf: Studies of Oxidant Mechanisms

Investigators:

B. González-Flecha

Institution:

Harvard School of Public Health

Description and Objectives of Research:

A primary mechanistic hypothesis by which ambient air particles have a significant negative impact on human health is via the induction of pulmonary inflammatory responses mediated through the generation of reactive oxygen species. The objective of this study was to evaluate whether air particulates interact directly with protective enzymes involved in oxidative stress responses.

Our EPA Center has supported the innovative studies of Dr. Beatriz González-Flecha and her colleagues on oxidant mechanisms of particles in the lung. Dr. González-Flecha and her colleagues completed and published a study confirming the role of oxidants in the inflammatory response to CAPs in adult rats (Rhoden et al. 2004).

Summary of Findings/Accomplishments:

We performed enzyme activity assays on four enzymes involved in oxidative stress responses (Cu/Zn superoxide dismutase, Mn superoxide dismutase, glutathione peroxidase and glutathione reductase) in the presence of particles of varying toxicities and found distinctive inhibition patterns (Hatzis et al. 2006). We demonstrated that particles interact directly and inhibit *in vitro* the specific activity of enzymes involved in oxidative stress response. Moreover, for the different particle types tested, the inhibitory capacity of the particulates on the selected enzymes correlates with the *in vivo* toxicity of the particles (MSHA < NIST < ROFA). Our findings suggest that the potential to generate oxidative stress of ambient particles may be determined, at least in principle, on the basis of the pattern of inhibition of the enzymatic activity of a carefully selected panel of enzymes. On the basis of these findings, we suggest a strategy for an enzyme bioassay that could be used to assess the potential of particles to generate ROS-induced responses.

The experimental protocol included exposures to filtered air (sham) or CAPs aerosols (CAPs, 5 hours exposure, average mass concentration of $1100 \pm 300 \text{ g/m}^3$) in the presence or absence of 50 mg/Kg N-acetyl cysteine (NAC). BAL, tissue and blood samples were collected 24 hours after exposure. The results of this study showed a dramatic increase of polymorphonuclear neutrophil (PMN) number in BAL as a result to CAPs exposures. This increase was mediated by oxidants, since pre-administration of NAC effectively prevented PMN influx into the lung

(Rhoden et al. 2004). Additional data support our hypotheses that CAPs promotes oxidant-mediated cardiac dysfunction and that autonomic activation after CAPs deposition in the lung is critical for CAPs cardiotoxicity. Adult Sprague-Dawley rats were treated with the 1-adrenoreceptor antagonist atenolol, the muscarinic receptor antagonist glycopyrrolate or saline prior to exposure to urban ambient particles (UAP) (United Agri Products, SRM 1649, 750 g/Kg). Thirty minutes after UAP instillation the animals were anesthetized and assayed immediately for cardiac levels of oxidants (in situ chemiluminescence: CL). Tissue samples were collected and assayed for edema. Intratracheal instillation of UAP led to significant increases in heart oxidants and edema. β -blockage by atenolol and muscarinic blockade by glycopyrrolate effectively prevented cardiac oxidative stress and damage. These observations were confirmed in a model of inhalation exposure to CAPs.

To determine the role of oxidants in the development of cardiac malfunction rats were treated with NAC one hour prior to UAP instillation or CAPs inhalation. NAC prevented changes in heart rate and heart rate variability in UAP-exposed rats (Rhoden et al. 2005). These data strongly suggests that PM exposure increases cardiac oxidants via autonomic signals and the resulting oxidative stress is associated with significant functional alterations in the heart.

Conclusions:

The research associated with this project found particle exposures inhibited the specific activity of enzymes involved in oxidative stress response, with the inhibitory capacity of the correlating with the *in vivo* toxicity of the particles. Additional work showed particulate exposures to be associated with increases in neutrophils, cardiac oxidants and edema. Resulting oxidative stress was associated with significant functional alterations in the heart.

Publications:

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3. Rhoden, C., G. Wellenius, E. Ghelfi, J. Lawrence and B. González-Flecha (2005). "PM-induced cardiac oxidative stress is mediated by autonomic stimulation." *Biochimica et Biophysica Acta* 1725: 305-313.

ADMINISTRATIVE CORE

Personnel:

L. Fox, P. Koutrakis, T. Mark, A. Smythe, H. Suh, J. Vallarino

The Administrative Core has been responsible for the overall coordination of the Center. This core includes administrative support, core secretarial support, fiscal management, central data management, quality assurance, internal Executive and External Advisory Committee meeting schedules, meeting organization, report preparation, and communication with EPA.

Dr. Petros Koutrakis has overseen all administrative and fiscal issues for the Center. He has been assisted by Alice Smythe, the Center Coordinator. All fiscal and administrative duties have been directed by Linda Fox, Center Administrator and Administrator of the Exposure, Epidemiology & Risk Program (EER). She has been responsible for overall budgetary issues and been liaison between HSPH and EPA for administrative/fiscal concerns, including providing annual budget summaries and expenditures, assurance of grant compliance, supervising payroll and non-payroll expenditures, assisting with subcontracts and other required reports. Ms. Fox has been assisted by Ms. Tracy Mark, her financial administrative assistant and others in the EER Program Office. Interactions were also necessary with administrative staff in other collaborating units within the School.

The research staff at Harvard University has had considerable experience working with large exposure, epidemiological, and toxicological data sets. While the principal investigators had responsibility for processing and analyzing data for their individual projects, data from each of the projects were stored and managed centrally, with Dr. Helen Suh overseeing the data management. Finally, Jose Vallarino, a Research Specialist at HSPH, has served as the Center's quality assurance officer. He has had considerable experience preparing and reviewing laboratory and field protocols and quality control procedures.

RESEARCH COORDINATION CORE

Investigators:

D. Dockery, P. Koutrakis, F. Speizer

The Research Coordination Core was responsible for defining, coordinating, and integrating all research conducted as part of the Center and was led by Dr. Dockery. A key aspect of the Center was its intention to have an ongoing and continual evaluation of research needs and priorities. To achieve this goal, the Center included a rigorous and multi-phased research coordination and evaluation process, which was developed based on our experience from over twenty years of multi-disciplinary collaborations in air pollution health effects. This coordination and evaluation process drew upon experts from a wide range of disciplines at the Harvard School of Public Health and the Harvard Medical School, as well as experts from outside agencies, universities, and other organizations that provided focused and timely responses to current and evolving questions about airborne particulate matter. Specifically, experts from six internal and external groups contributed to the research coordination and evaluation process and determined the direction and coordination of PM research that was conducted at the Center. These groups included: the National Research Council, the External Science Advisory Committee, the consortium of EPA Airborne Particulate Matter Centers, the Working Group on PM Exposures and Health Effects, the Working Group on Research Strategy Evaluation, and the Steering Committee at the center at Harvard. Their contributions to the research coordination and evaluation process are described below.

National Research Council. The National Research Council panel on Research Priorities for Airborne Particulate Matter was an important source of direction for the Center. In fact, the Center's proposed ten initial projects were developed to address the immediate research priorities listed in NRC's report entitled "Immediate Priorities and Long-Range Research Portfolio." The Center was fortunate to have two investigators, Drs. Koutrakis and Speizer, as members of the NRC Expert panel. As a result, direct and immediate access to panel deliberations was available to Center investigators and was used to decide the Center's future research priorities and directions.

External Advisory Committee. A multi-disciplinary External Advisory Committee of distinguished scientists was established to provide input into both ongoing and future research directions. The Advisory Committee was comprised of experts in a range of disciplines, including atmospheric chemistry, exposure and risk assessment, policy, biostatistics, epidemiology, cardiac and respiratory health, and toxicology. Some committee members were recruited from other PM Centers to foster and facilitate exchange and collaborations. The Committee met annually for two days to formally review the Center activities. The first meeting day was devoted to the traditional presentation of study designs and results, and was followed by a structured workshop on the second day to define research needs and priorities. This workshop would include both the Committee members and the Center investigators.

Consortium of EPA Airborne Particulate Matter Centers. As one of EPA's PM Centers, we approached the other Centers to form a consortium of PM Centers. The specific aims of this Consortium were to ensure that research in each Center was coordinated with, complementary to, and not redundant with that of other EPA PM Centers, and to facilitate rapid dissemination of research findings and other information between Centers, the EPA, the rest of the scientific community, and the lay public. To achieve these specific aims, the Consortium organized an annual colloquium to review particulate matter research. As part of this colloquium, representatives from each of the EPA-sponsored Centers would participate in a structured meeting to plan and coordinate research activities. Through the Consortium, the EPA Centers established linked sites on the Web to provide descriptions of current research programs, downloadable copies of research reports and publications, and access to extended summaries and original data.

Harvard Working Group on PM Health Effects. A previously established Working Group on PM Health Effects would meet bi-weekly to encourage informal interactions between the Center investigators. This group was formed several years prior and included experts in exposure and risk assessment, epidemiology, toxicology, clinical medicine and physiology. The PM Center at Harvard established a formal structure for this working group and provided core support for its activities.

Working Group on Evaluation of Research Strategies. We used a formal decision and value of information analysis of particulate matter control and research to guide our decisions about future research activities. This analysis was based on the concept of the value of information (i.e., the expected value of the likely consequences of suboptimal decisions) as a measure of the costs of current levels of uncertainty. To implement our future research evaluation process, we characterized quantitatively the current risk uncertainties and developed estimates of the informativeness and cost of alternative research strategies.

Most of these approaches were based on frequentist notions of probability and standard approaches for analysis of the propagation of uncertainty (e.g., Gauss' law, lognormal error analysis, or Monte Carlo simulation). Model uncertainty was determined through the use of formally elicited expert judgment.

Steering Committee at the PM Center at Harvard. The PM Center at Harvard was directed by a Steering Committee consisting of the Center Director, the two Co-Directors, and the Principal Investigators of the research projects and cores. Dr. Koutrakis, the Principal Investigator, chaired the Steering Committee. The Steering Committee was responsible for the overall direction, coordination, and integration of the research conducted by the Center. It established research priorities and directions based on recommendations from external groups, including the National Research Council, the External Advisory Committee, the Consortium of PM Centers, the Harvard Working Groups on Particle Health Effects and Evaluation of Research Strategies. The Steering Committee met at least quarterly to monitor progress, identify new research initiatives, and coordinate research with other Centers.

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Effects - Intercomparison of Results and Implications. Environmental Health Perspectives 2005; 113(12):1768-74.

ANALYTICAL AND FACILITIES CORE

Investigators:

J. Godleski, P. Koutrakis, M. Wolfson, P. Demokritou

The Analytical and Facilities Core of the PM Center supported the development of a wide variety of technologies useful for Center Projects and also useful for other studies of particle health effects, all of which have resulted in peer-reviewed publications, or have manuscripts currently in preparation. Two especially important technologies are the multi-pollutant sampler and the ultrafine particle concentrator, which are described briefly below, along with a summary description of the other technologies.

Multipollutant Sampler. A personal multipollutant sampler has been developed that can be used for measuring exposures to particulate matter and criteria gases. The system uses a single personal sampling pump that operates at a flow rate of 5.2 liters per minute (LPM). The basic unit consists of two impaction-based samplers for PM_{2.5} and PM₁₀ attached to a single elutriator. Two mini PM_{2.5} samplers are also attached to the elutriator for OC, EC, sulfate, and nitrate measurements. For the collection of nitrate and sulfate, the minisampler includes a miniaturized honeycomb glass denuder that is placed upstream of the filter to remove nitric acid and sulfur dioxide and to minimize artifacts. Two passive samplers can also be attached to the elutriator for measurements of gaseous copollutants such as O₃, SO₂, and NO₂. The performance of the multipollutant sampler was examined through a series of laboratory chamber tests. The results showed good agreement between the multipollutant sampler and reference methods. The overall sampler performance demonstrates its suitability for personal exposure assessment studies.

Ultrafine Particle Concentrator. The ultrafine particle concentrator produces exposure atmospheres for toxicological testing that have concentrations increased above ambient levels by a factor of 40 to 50. This method involves condensational growth (with supersaturated water vapor) to sizes large enough to concentrate using a two stage virtual inertial impactor. Following being concentrated in the impactor, a thermal dryer is used to remove condensed water and restore the particles to their original sizes. Validation tests showed that, with an optimum supersaturation ratio, all ultrafine particles grow and get concentrated by about the same enrichment factor, regardless of their composition and surface properties. This system delivers 58 LPM of concentrated aerosol that can be used for *in-vivo* or *in-vitro* inhalation toxicological studies.

Other Technologies. Several of the new technologies developed by this Core employ conventional inertial impactors for size-selective collection of particles that use the polyurethane foam impaction substrates previously developed by the Aerosol Properties Laboratory at Harvard, including the following:

- 1) High Volume Cascade Impactor for Toxicological and Chemical Characterization Studies;

- 2) Compact Multistage (Cascade) Impactor for the Characterization of Atmospheric Aerosols;
- 3) Impactor for a PM_{2.5} Speciation Sampler;
- 4) High Loading PM_{2.5} Speciation Sampler, and;
- 5) Personal Cascade Impactor.

Other technologies developed by this Core employ inertial virtual impactors to separate particles by size, while keeping them suspended in air, including the High Volume Coarse Particle Concentrator and the Dichotomous Slit Nozzle Virtual Impactor.

A novel technological system was also developed by this Core for continuous measurements of ambient particle deposition in human subjects. Three other new technologies were developed by this Core for the TERESA study, including:

- 1) a system for the toxicological evaluation of particles generated from coal-fired power plants;
- 2) a photochemical chamber for the toxicological study of coal combustion emissions, and;
- 3) a counter-current parallel plate membrane denuder for the nonspecific removal of gases from an aerosol stream.

TECHNOLOGY DEVELOPMENT AND TRANSFER CORE

Investigators:

B. Coull, P. Demokritou, P. Koutrakis, J. Lawrence, M. Wolfson, J. Schwartz

The Technology Core led by Dr. Koutrakis focused on implementation and integration of the new technologies into the work of researchers at Harvard and a number of other research centers. In conjunction with the analytical and facilities core, we supported a number of exposure assessment studies through the development and provision of state-of-the-art personal, microenvironmental, and outdoor particulate and gaseous samplers. This core also supported use of the instruments in toxicological studies by operating and servicing the concentrator and by developing new concentrator technologies. As new particle samplers and generating systems were developed, they were made available to other Centers and research groups. We published a number of research papers documenting the performance of these instruments (Demokritou et al. 2003, Demokritou et al. 2004a, Gupta et al. 2004), and we assisted a number of research groups in installation and operation of these systems (Savage et al. 2003). These studies have already substantially improved our understanding of particle health effects.

Publications:

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Publications List

The following publications were produced with support from the EPA Center for Particle Health Effects at Harvard.

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