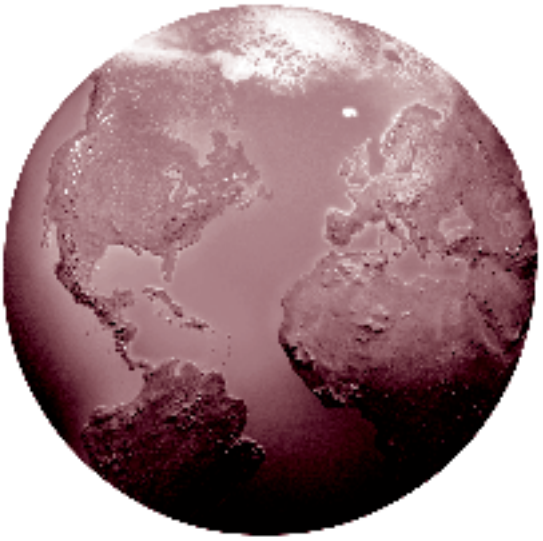

HEALTH EFFECTS INSTITUTE

ANNUAL CONFERENCE 2006

Program and Abstracts

25 Years

Trusted Science • Cleaner Air • Better Health

April 9–11, 2006

Palace Hotel
San Francisco

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HEALTH EFFECTS INSTITUTE

2006 Annual Conference

Palace Hotel
San Francisco, CA
April 9–11, 2006

HEI Conference Program

Sunday, April 9

11:30–12:45 Lunch

1:00 Opening *Dan Greenbaum*, Health Effects Institute

1:05 Science and Standard Setting
Chairs: *Alan Lloyd,* California Environmental Protection Agency; and *Robert Maynard*, Department of Health, London

How are health effects studies interpreted by local, national, and regional regulatory organizations (such as the California Air Resources Board, US Environmental Protection Agency, European Union, International Agency for Research on Cancer, and World Health Organization)? How are the resulting standards and guidelines used to (1) estimate and communicate risk, and (2) improve air quality and protect human health? These questions are discussed with a focus on PM standards.

1:05 **The Use of Ambient Air Standards: A Global Overview**
Robert Maynard

1:30 **Issues of Reporting Standards vs Concentration Response Functions**
Kirk Smith, University of California, Berkeley, and HEI International Scientific Oversight Committee

2:00 **Using Epidemiological Evidence and Air Quality Data to Inform Air Pollution Guidelines**
Sverre Vedal, University of Washington and HEI Review Committee

2:30 Break

SETTING AND USING AMBIENT AIR STANDARDS TO IMPROVE AIR QUALITY AROUND THE WORLD

2:50 **Asia**
Supat Wangwongwatana, Thailand Pollution Control Department

3:05 **Europe**
Michal Krzyzanowski, WHO European Centre for Environment and Health

3:20 **United States**
Lydia Wegman, US Environmental Protection Agency

3:35 **Discussion**

3:50 **Concluding Remarks**
Alan Lloyd

4:00–6:00 Poster Session I
Posters highlight ongoing HEI research on particulate matter, gaseous pollutants, diesel exhaust, and air toxics; these studies are complemented with research supported by other organizations (see page 7).

6:15 Opening Reception, Dinner, and Celebration:
25 Years of Trusted Science for Better Air Quality Decisions

Monday, April 10

7:00–8:00 Breakfast

8:10 Hot Topics: Breaking News

Chairs: *Mark Utell,* University of Rochester Medical Center, and Chair, HEI Research Committee; and *Daniel Tosteson,* Harvard Medical School, and Chair, HEI Review Committee

New HEI programs and projects are highlighted, as are emerging technologies that may affect future vehicular emissions.

8:10 **Introduction** *Chairs*

8:20 **Preview of Special Report on Mobile-Source Air Toxics**
Tom Kensler, Johns Hopkins Bloomberg School of Public Health

9:00 **Upcoming HEI Reports**
Sverre Vedal

9:25 **New HEI Research Programs: Accountability, PM, Testing of Advanced Diesel Engines (ACES)**
Jane Warren, Health Effects Institute

9:50 **EMERGING TECHNOLOGIES**
Engine and After-Treatment Technologies to Reduce Diesel Emissions
Wayne Eckerle, Cummins Inc

California Diesel Retrofit Program for Vehicles
Annette Hebert, California Air Resources Board

10:30 Break

10:45–12:45 Poster Session II

Posters highlight ongoing HEI research on particulate matter, gaseous pollutants, diesel exhaust, and air toxics; these studies are complemented with research supported by other organizations (see page 11).

12:30–1:55 Lunch

2:00 Transboundary Migration of Air Pollution

Chairs: *Kenneth Demerjian,* SUNY Albany, and HEI Research Committee; and *Michael Brauer*, University of British Columbia, and HEI International Scientific Oversight Committee

Atmospheric pollutants recognize no borders or boundaries. Thus, pollution from one region or country may influence the levels of pollution and affect health in other areas. This session will examine global and regional atmospheric pollution, and the nature of long-range pollutant transport that spans cities, states, countries, and continents. Recent advances in spatial modeling and impact analysis, as they apply to micro and macro scale distances, will be described. Case studies that showcase research on transboundary areas will be presented.

2:00 **Introduction**
Kenneth Demerjian

2:10 **Spatial Movement of Pollution**
Dan Jaffe, University of Washington

2:40 **Source and Receptor Models to Understand Air Pollution Transport**
Jeffrey Brook, Environment Canada

3:10 **Health Implications of Long-Range Transport of Air Pollutants**
Denise Mauzerall, Princeton University

3:45 Break

4:10 **Transboundary Studies**
Amanda Wheeler, Health Canada
John Spengler, Harvard School of Public Health
Fernando Holguin, Emory University and Centers for Disease Control and Prevention

5:15 **Concluding Remarks**
Michael Brauer

5:30 Adjourn

EVENING FREE

Tuesday, April 11

6:30–7:45 Breakfast

New Research on the Health Effects of Air Pollutants: Part I

8:00 PM and Gaseous Pollutants

Chairs: *Mark Utell*; and *Ross Anderson,* University of London, and HEI Review Committee

Different perspectives will be presented on the possible roles of gaseous pollutants that have emerged from recent studies of the health effects of air pollutants. Among the topics to be discussed are the results of studies and analyses that suggest that ozone's effects are independent from those of PM; a review of current knowledge about the effects of sulfur dioxide; and the atmospheric chemistry of nitrogen dioxide and contrasting views on its role as an air pollutant.

8:00 **Introduction: Possible Pathways of Injury by Air Pollutants**
Mark Utell

8:15 **Ozone: Short-Term Effects on Mortality**
Michelle Bell, Yale University

8:45 **OZONE: LONG-TERM EXPOSURE AND LUNG FUNCTION**
A Study in Young Adults
Ira Tager, University of California, Berkeley

The Southern California Children's Health Study
John Peters, University of Southern California

9:25 **Discussion**

9:45 Break

10:15 **Update on Sulfur Dioxide: Its Health Effects and Its Role as a Surrogate Exposure Index for Other Toxicants**
Morton Lippmann, New York University

10:45 **Nitrogen Dioxide: A Surrogate of Traffic or a Pollutant in Its Own Right? A Brief Review of Evidence**
Frank Kelly, University of London

11:15 **Nitrogen Dioxide: Sources, Air Quality, and Chemistry in the Atmosphere**
Kenneth Demerjian

11:45 **Concluding Remarks**
Ross Anderson

12:00–12:45 Lunch

New Research on the Health Effects of Air Pollutants: Part II

1:00 PM Components

Chair: *Rogene Henderson,* Lovelace Respiratory Research Institute

Recent systematic efforts by HEI and others aim to examine and compare the toxicity of different PM components and characteristics. Speakers will discuss the diverse mechanisms and outcomes that have been associated with exposures to chemical components and physical characteristics of particles in epidemiologic and experimental studies. The session concludes with a perspective on how to integrate information on the effects of gaseous pollutants and PM into a common framework.

1:00 **Cardiovascular Effects of Components**
Mark Frampton, University of Rochester Medical Center

1:30 **Effects of Metals**
Dan Costa, US Environmental Protection Agency

2:00 **Effects of Coarse Particles**
Michael Lipsett, California Department of Health Services

2:30 **Integrating the Effects of Pollutant Gases and PM Components**
Mary Ross, US Environmental Protection Agency

3:00 Conference Adjourns

POSTER SESSION I

Sunday, April 9, 4:00–6:00

Accountability

HEI has initiated a new research program of accountability studies designed to evaluate the impact on health of regulations and other actions to improve air quality. Six HEI-funded accountability studies are already in progress and others are likely to start soon. **Dr Dockery** is evaluating the effects of a ban on coal sales in the 1990s on air pollutant concentrations, mortality rates, and hospital admission rates in 11 cities in Ireland. **Dr Peters** is evaluating the effect of social and economic changes in Eastern Germany during the 1990s on the ambient pollutant mixture and mortality rates. Two studies led by **Dr Kelly** take advantage of efforts to decrease traffic in London. One study will compare air pollutant concentrations and PM toxicity before and after the introduction of a congestion charging scheme that was implemented in 2003 to reduce traffic in Central London. His other study will assess the impact of designating Greater London as a Low Emission Zone (LEZ) in which the entry of the oldest and most polluting vehicles is restricted. Dr Kelly is currently collecting baseline air quality measurements in anticipation of the implementation of the LEZ in 2008. **Dr Morgenstern's** study is evaluating the impact of a major US regulation to reduce emissions from power plants east of the Mississippi River (Title IV of the Clean Air Act Amendments of 1990). The initial focus will be on the relation between the regulation and changes in emissions and on how changes in emissions relate to changes in air quality. **Dr Peel's** study expands on a previous assessment of the impact of reduced traffic and air pollution levels during the 1996 Summer Olympic Games in Atlanta. She is conducting a comprehensive assessment of the impact of reduced air pollution on cardiorespiratory health outcomes, including emergency department visits and arrhythmic events.

Two accountability studies not funded by HEI are included in this session. **Dr Liu's** study compares diesel exhaust exposures and health outcomes in children before and after the diesel school bus fleet in the Seattle area was retrofitted with oxidation catalysts, diesel particulate filters, and closed crankcase ventilation to decrease emissions. **Dr Tager** will present results from his study that evaluates the relations between decreases in the levels of individual and groups of air pollutants in the South Coast Air Basin from 1980–2000 with the rates of cause-specific mortality and morbidity for diseases associated with ambient levels of air pollution. The study is also estimating the economic value of any health benefits found to be associated with improved air quality over that period.

Effect of Sequential Irish Bans on Coal Sales on Hospital Admissions. DW Dockery, PG Goodman, L Clancy, ME Fay, and A Wilson

Improved Air Quality and Its Influences on Short-Term Health Effects in Erfurt, Eastern Germany. M Stölzel, S Breitner, J Cyrys, M Pitz, G Wölke, J Heinrich, W Kreyling, H Küchenhoff, H-E Wichmann, and A Peters

Congestion Charging Scheme in London: Assessing Its Impact on Air Quality and Health. FJ Kelly, HR Anderson, B Armstrong, R Atkinson, B Barratt, S Beevers, D Cook, R Derwent, S Duggan, D Green, IS Mudway, and P Wilkinson

The London Low Emission Zone Baseline Study. FJ Kelly, HR Anderson, B Armstrong, R Atkinson, B Barratt, S Beevers, D Cook, R Derwent, D Green, IS Mudway, and P Wilkinson

Accountability Analysis of Title IV of the 1990 Clean Air Act Amendments. RD Morgenstern, W Harrington, AJ Krupnick, M Bell, and J-S Shih

Impact of Improved Air Quality During the 1996 Atlanta Olympic Games on Multiple Cardiorespiratory Outcomes. JL Peel, M Klein, WD Flanders, JA Mulholland, and PE Tolbert

***Assessing Children's Exposures to Diesel Exhaust from Commuting by Diesel School Buses Before and After Diesel Engine Retrofit.** L-JS Liu, W Webber, J Sullivan, L Sheppard, J Kaufman, J Lewtas, and TS Hallstrand

***A Study to Evaluate Improvements in Health Outcomes from Incremental Improvements in Air Quality in Southern California.** IB Tager, R Neugebauer, F Lurmann, J Hall, and V Brajer

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* Study not funded by HEI.

Particulate Matter: Health Effects in Epidemiologic Studies

Contributions of different pollution sources and differences in factors such as weather and topography cause the air pollutant mixture to vary greatly in different regions of the United States and throughout the world. Such variations in the air pollutant mix may affect its toxic effects. HEI is funding several epidemiologic studies on air pollution and health in North America, Latin America, Europe, and Asia that will help to address whether health effects of exposure vary as the air pollution mixture varies across geographic regions.

Studies in North America, Latin America, and Europe

Two ongoing cohort studies funded by HEI are evaluating long-term effects of different pollutant mixtures. **Dr Brunekreef's** study is assessing traffic-related pollutant concentrations and estimating mortality from respiratory and cardiovascular causes among residents in the Netherlands. **Dr Krewski's** study is evaluating the long-term effects of air pollution on mortality among a subcohort of the American Cancer Society Study in a large population center, New York City.

Dr Bell, a recipient of HEI's Walter A Rosenblith New Investigator Award in 2004, is developing analytic methods to better evaluate the effects of various components of the PM mixture on cause-specific mortality in time-series studies.

Air Pollution and Health: A Combined European and North American Approach (APHENA) is a large, two-part, time-series study, led by **Drs Samet and Katsouyanni**, that is jointly funded by HEI and the European Commission. The APHENA study includes data from 9 Canadian Cities, the 32 European cities that were included in the study *Air Pollution and Health: A European Approach (APHEA)*, and the 90 US cities in the HEI-funded *National Morbidity, Mortality, and Air Pollution Study (NMMAPS)*. The monitoring of daily PM concentrations in several cities and the variation in pollutant mixture across continents and countries have allowed the APHENA investigators to explore and develop new analytic methods to evaluate the relation between exposures and health effects.

The goal of **Dr Romieu's** study is to use a common analytic framework to examine the association between daily levels of air pollution and health outcomes in several Latin American and Caribbean cities.

Long-Term Effects of Traffic-Related Air Pollution on Respiratory and Cardiovascular Mortality (NLCS-AIR Study). RMJ Beelen, G Hoek, PH Fischer, PA van den Brandt, RA Bausch-Goldbohm, and B Brunekreef

Particulate Air Pollution and Mortality in New York City. M Jerrett, RT Burnett, K Ito, G Thurston, Z Ross, E Hughes, CA Pope III, R Ma, EE Calle, MJ Thun, and D Krewski

National Factor Analysis of Particulate Matter Chemical Speciation Data. ML Bell, K Ebisu, and F Dominici

Air Pollution and Health: A Combined European and North American Approach (APHENA). JM Samet, K Katsouyanni, RD Peng, and E Samoli

Multi-City Study of Air Pollution and Health Effects in Latin America. I Romieu, N Gouveia, and L Cifuentes

Studies in Asia

The *Public Health and Air Pollution in Asia (PAPA)* program continues its commitment to bring independent science on the health effects of air pollution in Asian cities to government policymakers, industry, and other stakeholders in the developing countries and emerging markets of Asia. Funding to HEI for this program comes from the US Agency for International Development (USAID), foundations, and industry; HEI and the Clean Air Initiative for Asian Cities work cooperatively to support the program. As the seven time-series studies on the health effects of short-term exposure to air pollution in Asian cities progress, the scientific and technical capacities of a growing network of Asian investigators continue to develop.

Investigators have completed collection and validation of health and air pollution data for their city-specific studies in China and Thailand. They are now working on data analysis and statistical modeling. Studies led by **Dr Kan** in Shanghai, **Drs Qian and He** in Wuhan, and **Dr Vichit-Vadakan** in Bangkok focus on daily mortality. **Dr CM Wong's** study in Hong Kong assesses mortality and hospitalizations for respiratory illness, and also explores methods to evaluate the interaction between air pollutants and influenza virus on mortality. **Dr Wong** is also

leading the joint effort to complete a common protocol for a future coordinated second-stage analysis across the first four Asian cities studied (ie, Shanghai, Wuhan, Bangkok, and Hong Kong).

The three time-series studies in India (**Dr Balakrishnan** in Chennai (formerly Madras), **Dr Kumar** in Ludhiana, and **Dr Uma** in Delhi) focus on the impact of air pollution on mortality from natural causes. These investigators have completed collection of health and air pollution data, and are now in the process of validation and preliminary analyses of the data.

A Time-Series Study of Ambient Air Pollution and Daily Mortality in Shanghai, China. H Kan, B Chen, N Zhao, Y Zhang, G Song, C Guo, G Chen, and D Xia

Modification of Extreme Hot Weather on Effects of Ambient Particle Pollution on Cause-Specific Mortality in Wuhan, China. Z Qian, Q He, HM Lin, D Liao, CM Bentley, L Kong, D Zhou, W Liu, N Yang, J Dan, S Xu, F Xu, and B Wang

Estimating the Mortality Effects of Air Pollution in Bangkok, Thailand. N Vichit-Vadakan, B Ostro, N Vajanapoom, W Aekplakorn, and S Wangwongwatana

Interaction Between Air Pollution and Respiratory Viruses: Time-Series Studies for Daily Mortality and Hospital Admissions. CM Wong, JSM Peiris, TQ Thach, PYK Chau, KP Chan, RY Chung, GN Thomas, TH Lam, TW Wong, and AJ Hedley

Public Health and Air Pollution in Asia (PAPA)—A Multi-City Study for Short-Term Effects of Air Pollution on Mortality. N Vichit-Vadakan, B Ostro, N Vajanapoom, W Aekplakorn, S Wangwongwatana, CM Wong, JSM Peiris, TQ Thach, PYK Chau, KP Chan, RY Chung, GN Thomas, TH Lam, TW Wong, AJ Hedley, BH Chen, HD Kan, NQ Zhao, GX Song, GH Chen, ZC Shan, CY Guo, ZM Qian, QC He, HM Lin, LL Kong, NN Yang, WS Liu, DJ Zhou, DP Liao, and JJ Dan

Developing Exposure–Response Functions for Air Pollutants from Time-Series Analyses—A Pilot Exercise in Chennai, India. K Balakrishnan, B Ganguli, S Sankar, S Gosh, D Rajagopalan, and V Thanasekaraan

Time-Series Study of Air Pollutants and Mortality in Ludhiana City, India
R Kumar, SK Jindal, GPI Singh, JS Thakur, S Sharma, SPS Bhatia, ML Garg, and HK Parwana.

Time-Series Study on Air Pollution and Mortality in Delhi, India. R Uma, KS Nairy, K Chhabra, GC Kilnani, D Caussy, M Seghal, and S Raghvan

Particulate Matter: Emissions, Particle Chemistry, and Biological Effects Studies

HEI is funding several studies that examine the properties of emissions from different sources and investigate the properties of particles that affect health. A key issue in trying to evaluate the effects of air pollutants is the chemical transformation that pollutants undergo in the atmosphere. Such transformations can yield new chemical species that may affect the reactivity of the pollutant mix. Another crucial issue is the profound influence that particle characteristics such as chemical reactivity, size, and solubility may have on the fate of particles after they have been inhaled.

In addition to evaluating these issues, HEI is funding several studies that examine the pathophysiologic effects of exposure to particles in different biological systems—in particular, the cardiovascular and respiratory systems.

Dr Zielinska's study is designed to evaluate chemical and physical changes of airborne components of diesel exhaust and to test the toxicity of these transformed products in vivo and in vitro. **Dr Baum's** study will investigate the emission rates of chemically reduced nitrogen compounds, a group of toxic chemicals (including hydrogen cyanide and nitrosamines) that are found in emissions from light-duty motor vehicles. He will develop analytical methods to detect low levels of these compounds and measure ambient levels and emission rates from stationary and on-road vehicles.

Dr Kendall, a recipient in 2004 of HEI's Walter A Rosenblith New Investigator Award, is evaluating the interaction of particles with surfactant proteins in lung fluid, an important aspect of particle deposition and retention in the lung. **Dr Kennedy** is investigating the effects that particle size, surface charge, and composition (focused on pure metal oxide nanoparticles of cerium, iron, zinc, and yttrium) have on particle uptake and the induction of

inflammatory responses in human aortic endothelial cells in vitro. **Dr Nurkiewicz**, a recipient in 2005 of HEI's Walter A Rosenblith New Investigator Award, is studying the mechanism by which exposure to PM contributes to increased cardiovascular disease by assessing the effects of inhaled fine and ultrafine titanium dioxide particles on systemic microvascular circulation in rats.

Dr Aust is determining whether exposure to iron in inhaled coal fly ash particles induces oxidative stress in rat lungs, whether intracellular levels of the iron-binding protein ferritin can be used to determine the bioavailability of iron, and whether measures of the inflammatory response in bronchoalveolar lavage fluid and blood correlate with the bioavailability of iron. Using previously recorded, continuous, 24-hour electrocardiogram recordings from older individuals, **Dr Lux** is assessing differences in ventricular repolarization during periods of low and high ambient particulate matter. Because changes in repolarization may play a role in the development of cardiac arrhythmias, results from the study may provide information about whether pollution-induced changes in repolarization can be used as a marker of increased arrhythmia risk. **Dr Oldham** is using existing lung casts of a mouse model of asthma to obtain airway morphometry data. These data will be put into a stochastic dosimetry model to compute the deposition efficiency of particles over a large size range. He will also compare the dosimetry predictions obtained in this model with predictions in other strains of mice and in humans.

Atmospheric Transformations of Diesel Emissions. B Zielinska, J Sagebiel, S Samy, J McDonald, JC Seagrave, P Wiesen, and K Wirtz

Significance of Highly Toxic Secondary Emissions from On-Road Vehicles. MM Baum, RD May, JA Moss, and GA Poskrebyshev

Nanotoxicology of Fine PM. M Kendall

Induction of Vascular Endothelial Inflammatory Response by Metal Oxide Nanoparticles. A Gojova, B Guo, RS Kota, JC Rutledge, IM Kennedy, and AI Barakat

Peripheral Microvascular Dysfunction Follows Ultrafine Titanium Dioxide Inhalation. TR Nurkiewicz, DW Porter, M Barger, AF Hubbs, L Millecchia, K Rao, BT Chen, D Frazer, V Castranova, and MA Boegehold

Pulmonary and Systemic Effects of Inhaled Coal Fly Ash in Rats. KR Smith, JM Veranth, UP Kodavanti, AE Aust, and KE Pinkerton

Air Pollution Effects on Ventricular Repolarization. RL Lux and CA Pope

Dosimetry Predictions in a Murine Animal Model of Human Disease. MJ Oldham

POSTER SESSION II

Monday, April 10, 10:45–12:45

Air Toxics: Hot Spot and Carbonyl Studies

Hot Spot Studies

Evaluating the magnitude of exposure of the population to air pollutants is a crucial step in the process of risk evaluation. HEI and other institutions are funding research projects to measure personal exposure to air pollutants and to evaluate the relation between personal occupational and residential exposure measurements and measurements collected at monitoring sites. Environmental exposure to air toxics is relatively low compared with exposure to criteria pollutants regulated by US National Ambient Air Quality Standards. Nevertheless, the potential for widespread long-term exposure and the large proportion of the population exposed to air toxics have led to concerns regarding their possible health effects. Many of the predictions of health risks from exposure to ambient air toxics are based on modeled estimates of exposure. To overcome the uncertainties of such estimates, HEI is funding five studies (**Drs Fujita, Harrison, Lioy, Smith,** and **Spengler**) that measure personal, occupational, and residential exposure in highly exposed populations, such as those working or living in areas that are designated as hot spots because both industrial and mobile air pollutant sources are present. The data from these studies will contribute to better understanding of the intensity of and variations in personal and ambient exposure to air toxics derived from mobile and other sources.

HEI is also funding one other study at a hot spot location. **Dr Ferro** is characterizing PM particles using measurements collected from personal monitors worn by residents, as well as from fixed and mobile monitors near the Peace Bridge Plaza Complex where Dr Spengler's study is being conducted.

In addition to these studies, **Dr Pingitore** is presenting a study relevant to air toxics and hot spots (funded by the National Institute of Environmental Health Sciences). It examines the relation between air and environmental quality at the neighborhood level, and the incidence and prevalence of asthma among the largely Mexican-American population of the border city of El Paso TX.

Assessing Exposure to Air Toxics in Microenvironments Dominated by Mobile Sources. EM Fujita, DE Campbell, and B Zielinska

Measurement and Modeling of Exposure to Air Toxic Concentrations for Health Effect Studies and Verification by Biomarker (MATCH Project). RM Harrison, S Harrad, S Vardoulaki, J-M Delgado, S Baker, C Meddings, N Aquilina, I Matthews, R Anderson, and B Armstrong

Ambient and Personal Exposures to Air Toxics in Camden NJ. Z Fan, X Zhu, J Zhang, P Georgopoulos, SW Wang, PA Ohman-Strickland, PJ Lioy, JL Held, and LJ Bonanno

Air Toxics Hot Spots and Traffic Exposures. TJ Smith, ME Davis, J Hart, F Laden, and E Garshick

Spatial Distribution of Air Toxics Near a US Border Crossing. SJ Newberg, J Vallarino, S Melly, J Lwebuga-Mukasa, S Chillrud, and JD Spengler

Characterization of Primary and Secondary Particles and Associated Personal Exposures Near a Major International Trade Bridge Between the US and Canada. AR Ferro, C Schreiner, TR McAuley, and PA Jaques

***Childhood Asthma and Respiratory Health in Latino Children in the El Paso Airshed.** NP Pingitore, M Amaya, W-W Li, R Currey, S Burchiel, and M Berwick

* Study not funded by HEI.

Carbonyl Studies

HEI is funding two studies focused on acrolein and other carbonyls. Acrolein is a common irritant found in cigarette smoke and automobile exhaust. It has been notoriously difficult to measure acrolein at low concentrations in ambient air because the chemical complex formed to capture this compound is highly unstable. **Dr Cahill** has developed and tested a new mist-chamber method to measure exposure to acrolein and other carbonyls. **Dr Borchers**, a 2003 recipient of the Walter A Rosenblith New Investigator Award, is evaluating mechanisms underlying acrolein toxicity, focusing on the role of a subset of T lymphocytes in inducing inflammatory responses in mice exposed to acrolein via inhalation.

Determination of Acrolein and Other Toxic Carbonyls in Air for Exposure Assessment. VY Seaman and TM Cahill

T Cell Regulation of Acrolein-Induced Pulmonary Inflammation and Epithelial Cell Pathology. MT Borchers, N Harris, S Wesselkamper, and M Sartor

Particulate Matter Studies

Measuring and Modeling Exposure Studies

Studies will be presented that measure and evaluate PM components and compounds to which people are exposed in a variety of settings. One challenge is to measure low-level concentrations of the complex array of components of the pollution mixture and then to obtain accurate exposure estimates of individuals and populations.

Dr Schauer, a 2002 recipient of HEI's Walter A Rosenblith New Investigator Award, is exploring methods to characterize air toxic compounds (such as trace metals) found on particulate matter, including compounds from personal exposure samples, and to associate them with specific sources. **Dr Seigneur** compiled pollutant and other data collected at and near the EPA's $PM_{2.5}$ Chemical Speciation Trends Network (STN) sites. They have incorporated this information into a website, the HEI Air Quality Database, which is available to investigators to provide a user-friendly resource for health effects studies. **Dr Levy**, a recipient of HEI's Walter A Rosenblith New Investigator Award in 2005, is extending geographic information system (GIS) methods to better capture exposure to traffic-related air pollutants by combining indoor and outdoor speciated PM measurements, novel statistical techniques to allow for source apportionment, and refined GIS predictors of traffic and site characteristics.

Source Apportionment and Speciation of Particulate Matter for Exposure and Health Studies. JJ Schauer, MM Shafer, BJ Majestic, and RJ Sheesley

A Web-Based Database of Fine Particulate Matter and Related Data for Health Effects Studies. B Pun, C Seigneur, S-Y Chen, and M Sze

Using Geographic Information Systems and Questionnaire Data to Predict Indoor and Outdoor Concentrations of Traffic-Related Air Pollution. JI Levy, JE Clougherty, LK Baxter, and RJ Wright

Diesel Exhaust Health Effects Studies

HEI is funding several studies to evaluate the effects of diesel exhaust and other particles on the exacerbation of asthma and other airway allergic conditions. **Dr Diaz-Sánchez's** study evaluates whether inflammatory and immunologic changes are observed in the upper airways of allergic and asthmatic volunteers exposed to diesel exhaust. **Dr Zhang's** study is evaluating the effect that exposure to a major London thoroughfare with only diesel traffic has on volunteers with asthma; the study will assess pulmonary function and biomarkers of oxidative stress and inflammation. **Dr Harkema's** study is determining whether exposure to diesel exhaust or concentrated ambient particles enhances allergic response in sensitized rats, as well as whether the timing of exposure to particles affects this enhancement.

Dr Campen is evaluating whether water-soluble components of diesel exhaust have constrictive effects in veins and arteries from rodents. **Dr SS Wong's** pilot study is determining the effects of exposure to diesel exhaust particles on the expression of neutral endopeptidase in airway epithelial cells. This membrane-bound enzyme, which inactivates a variety of physiologically active peptides, is downregulated in some tumors.

Heterogeneity in Individual Airway and Immune Responses to Diesel Exhaust Suggests a Susceptible Subgroup. D Diaz-Sanchez, JW Miller, WS Linn, KW Clark, DR Cocker III, and H Gong Jr

Short-Term Exposure to Diesel Exhaust Leads to Asthma Worsening: Evidence from a Real-World Study. JE McCreanor, J Zhang, P Cullinan, MJ Nieuwenhuijsen, KF Chung, P Ohman-Strickland, JS Evans, E Malliarou, I Han, M Svartengren, and L Jarup

Disparate Allergic Airway Responses to Diesel Exhaust Inhalation During Allergen Sensitization Versus Allergen Challenge. JG Wagner, E Barrett, J McDonald, and JR Harkema

Diesel-Induced Venous Congestion and Vasoconstriction: A Potential Link to Heart Failure Symptoms. MJ Campen, T Knuckles, and AK Lund

Molecular Effects of Diesel Exhaust Particulates on Respiratory Neutral Endopeptidase in Carcinogenesis. SS Wong, NN Sun, ML Witten, LB Hersh, B Lu, and C Gerard

PM Components, Exposure Assessment, and Health Effects Studies Supported by Other Agencies

Dr Wexler will describe the work that his team, the San Joaquin Valley Aerosol Health Effects Center, will conduct for his EPA PM-Health Center grant to investigate the mechanistic links between ambient particles and the health effects they elicit. **Dr Wyzga** will present information on how to assess the role of organic carbon compounds in health effects studies. **Dr Ostro** will report the results of an epidemiologic study (CALFINE) funded by the California EPA that examined associations among 22 different components of $PM_{2.5}$ and daily mortality in six heavily populated California counties. **Dr Tager's** study, the Fresno Asthmatic Children's Environment Study (FACES), which is supported by the California Air Resources Board and the US EPA, is investigating whether the proximity of residence to highway traffic is associated with pulmonary function in children with asthma in Fresno CA. **Dr Luttinger's** study is evaluating temporal associations between air pollutants and asthma-related emergency department visits in New York City communities.

***The San Joaquin Valley Aerosol Health Effects Center—An EPA PM-Health Center.** AS Wexler, KE Pinkerton, MV Fanucchi, DW Wilson, and others

***Identifying the Role of Organic Compounds in Air Pollution/Health Studies.** RE Wyzga and A Rohr

***The Effects of Fine Particle Species on Daily Mortality in Six California Counties: Results from CALFINE** B Ostro, W-Y Feng, R Broadwin, S Green, and M Lipsett

***Highway Traffic Near Residence Associated with Altered Pulmonary Function Among Children with Asthma: Results from the Fresno Asthmatic Children's Environment Study** HG Margolis, JK Mann, FW Lurmann, KM Mortimer, JR Balmes, SK Hammond, and IB Tager

***Associations Between Air Pollutants and Asthma Exacerbations in New York City** GM Recer, PL Kinney, SA Hwang, and DA Luttinger

*Study not funded by HEI.

Pulmonary and Systemic Effects of Inhaled Coal Fly Ash in Rats

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Primary particle emissions of ash from coal-fired power plants are well controlled, but coal fly ash (CFA) can still represent a significant fraction of the overall particle exposure for some plant workers and highly impacted communities. We measured the effect of CFA on markers of pulmonary and systemic inflammation and injury in male Sprague-Dawley rats by nose-only exposure to CFA or filtered air, 4 hrs/day for 3 days. Average concentration of CFA in the $PM_{2.5}$ range was 1400 μg/m^3, of which 600 μg/m^3 was in the PM_1 range. Animals were examined 18 and 36 hours post exposure. The total number of neutrophils in bronchoalveolar lavage fluid (BALF) increased up to 5.5-fold above control values and there were also increases in blood neutrophils, MIP-2 in BALF, IL-1β in lung tissue, total antioxidant potential in lung tissue, and transferrin in BAL. Increases in total antioxidant potential likely reflect a compensatory response against reactive oxygen species and lung inflammation as reflected by altered BALF cell differential and pulmonary cytokines. The observed animal responses are consistent with the ability of CFA to induce oxidative stress leading to neutrophilic inflammation following short-term exposure. Primary mineral ash particles in the 0.4-2.5 μm size range from coal-fired power plants cause an influx of neutrophils and an increase in proinflammatory cytokines in the lung at occupationally relevant exposure levels. However, CFA particles do not appear to have unusual potency compared to published studies with concentrated ambient particles. This study contributes to understanding those mechanisms by which specific types of particulate air pollution affect human health.

Developing Exposure–Response Functions for Air Pollutants from Time-Series Analyses - A Pilot Exercise in Chennai, India

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This paper describes the protocol developed for the construction of the exposure and mortality time series for the purposes of developing a model to estimate acute effects of air pollutants in the greater Chennai metropolitan area (located in Southern India). Implications for the development of a common protocol for concurrent Indian and Asian studies under the PAPA program of HEI are also described.

Raw data on criteria air pollutants (PM 10, SO_2 and NO_x) recorded at the 8 ambient air quality monitoring stations operated by the Tamil Nadu State Pollution Control Board (TNPCB) was retrieved for the period 2002 to 2004. The mortality data for the corresponding period was retrieved from the Municipal Corporation of Chennai. 7 out of 8 sites met site selection criteria (outlined in the common PAPA protocol for the Asian cities in progress). Information on QA/QC parameters abstracted from raw field data cards for all stations was compared with criteria for inclusion of valid data points as per protocols of The Central Pollution Control Board (Govt. of India). Of the 9 months for which such checks have been completed no inconsistencies have been found thus far. Electronic mortality data was assessed for possible sources of biases while data transfer by cross checking electronic data with data recorded in death forms on file at the Corporation zonal offices. Only data on date of death, place of death, age and sex were found to be recorded with greater than 99% accuracy and it was decided to restrict the analyses to these parameters. Data on cause of death is being retrieved from another database maintained by the National Cancer Institute in the city (initially it will be limited to excluding intentional and accidental deaths).

Following the cleaning of the datasets, modeling was attempted to fit a Poisson additive regression of all cause mortality (excluding accidental deaths) on daily pollutant level after adjusting for other known risk factors like temperature and humidity. The main problem so far has been the construction of the exposure series. Previous studies have omitted monitors with > 25% missing data which is not feasible in Indian cities with most single monitors reporting a missing-ness of greater than 50% and most combinations yielding a missing-ness of 30 to 40%. Various parametric imputation methods such as, using ANOVA models, centering , distribution fitting, imputation through regression on other covariates and imputation using mortality data are being attempted as it was felt that such methods had the scope to correct the standard error of the final estimate of the pollution effect for uncertainty in the exposure values. Recently, data from a continuous air quality monitoring station co–located with a conventional air quality monitoring station has been provided that may provide crucial justification for imputing weekend values which had been completely absent in the earlier data sets. In addition, problems in employing the common PAPA protocol and suggested deviations necessary for the Indian set up are being studied.

Significance of Highly Toxic Secondary Emissions from On-Road Vehicles

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Catalytic converters have played a central role in reducing criteria pollutant exhaust emissions from light duty motor vehicles (LDMVs) and, herewith, improving air quality. However, side reactions on the catalyst surface produce secondary (i.e., post-combustion) unregulated emissions such as hydrogen cyanide, nitrous acid, nitrous oxide, and ammonia that have an adverse impact on human health and the environment. Of particular concern is a highly toxic class of compounds termed (chemically-)*reduced nitrogen compounds* (RNCs) that include hydrogen cyanide (HCN); *N*-nitrosamines (RR'NNO); amines (RR'NR"); hydrazine (H_2NNH_2); methylhydrazine [$CH_3(H)NNH_2$]; and hydroxylamine ($HONH_2$); as well as their reaction products with co-emitted aldehydes, where relevant. While these compounds have received little or no attention in the past, their presence in vehicle exhaust, even at low concentrations, could lead to significant adverse health effects, particularly in high exposure scenarios such as freeway communities, vehicle cabins, and enclosed spaces (e.g., residential and parking garages).

The overarching goal of this HEI-funded study is to investigate RNC emission rates from in-use LDMVs and to estimate the associated health risks. This objective addresses several Priority Topics (Air Pollution Mixture, Air Toxics, Mechanism of Effects) from HEI's Strategic Plan. Given that this is a new study, the poster presentation will describe the Year I activities, including the experimental design, namely:

1. Develop spectroscopic instrumentation. A tunable diode laser spectrometer for real-time, low-level HCN analysis will be developed and thoroughly evaluated in the laboratory;
2. Develop collection systems. Sorption cartridge methods for the collection of cyanohydrins, hydrazines, hydroxylamine, azines, hydrazones, oximes, and nitrosamines will be developed where standard methods do not exist. Wet effluent diffusion denuder samplers will be purchased for the collection of HCN, nitrous acid, ammonia, and amines;
3. Develop analysis methods. Analytical methods for the quantitative measurement of the above RNCs will be developed or adapted from the literature. These methods include: colorimetry, derivatization followed fluorescence detection, GC/MS, HPLC with UV-vis and MS detection, and IC with conductivity detection;
4. Evaluate efficiency, accuracy, and sensitivity. The efficiency of the above collection systems will be thoroughly evaluated in the laboratory. When methods do not meet target specifications, modifications will be made followed by further efficiency analysis;
5. Develop Library of standards. A comprehensive library of standards spanning all the RNCs of interest will be synthesized where commercial samples are not available. All the above standards will be fully characterized.

National Factor Analysis of Particulate Matter Chemical Speciation Data

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This project aims to connect particulate matter (PM) speciation data to health outcomes in order to assess which characteristics of PM are most detrimental to human health using data on PM speciation, weather, co-pollutant, and health outcome (e.g., mortality). This information could be used to determine what sources of PM emissions are most harmful. A better understanding of the toxicity of PM components and which sources are most damaging would allow more effective control of PM air pollution. Using PM speciation data derived from U.S. EPA data sources, we generated county-wide exposure estimates for 53 $PM_{2.5}$ components for 199 U.S. counties for the period 2000 to 2002. In development of the dataset, several key issues were identified including: suspect data, monitors with little data, extreme values, and co-location of monitors. We developed a protocol for combining data to generate county-wide averages. We performed factor analysis to identify common factors, or clusters of speciation components relating to: crustal materials, traffic, coal combustion, sea salt, oil combustion, and other combustion sources. Because any individual $PM_{2.5}$ component comes from a variety of sources and because this dataset is based on national data rather than a single community, it is difficult to label each factor as a definitive single source. This data set and factor analysis information will be linked to a Medicare hospital admissions data set.

T Cell Regulation of Acrolein-Induced Pulmonary Inflammation and Epithelial Cell Pathology

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Background: Acrolein exposure in mice causes macrophage influx to the airway lumen, accumulation of monocyte/macrophage and lymphocytes in the pulmonary interstitium, mucous cell metaplasia, epithelial cell damage, and airspace enlargement. Currently, the mechanisms that control these events are unclear. A novel role for γδ TCR^+ T cells in the regulation of inflammation and epithelial function has been reported following toxicant exposure, and preliminary data from our laboratory indicate that they are involved in the regulation of epithelial cell pathologies in response to repeated acrolein exposures. The objectives of this study are to assess the specific functions of pulmonary T cell subpopulations following acrolein exposure.

Methods: C57Bl/6J mice were exposed to 0, or 2.0 ppm acrolein 6h/d, 5 d/wk for 1 wk. αβ+ T cells and γδ+ T cells were isolated from the lung interstitium by modified collagenase digestion. Cells were purified by FACS sorting using antibodies against CD3 and TCRβ or TCRδ. Total RNA was purified and subject to two rounds of linear amplification. Microarray analyses were then performed to compare the similarities and differences between these two lymphocyte populations. We used the MAPPFinder program to dynamically link microarray data to the Gene Ontology (GO) hierarchy database.

Major Findings: 1) Acrolein exposure induced macrophage accumulation (2-3 fold) in the lungs of C57Bl/6J mice. Macrophage accumulation was attenuated in $\gamma\delta^{-/-}$ mice and was not observed in $\alpha\beta^{-/-}$ mice at all time points. Acrolein exposure increased the number of epithelial cells (primarily ciliated) recovered in the BAL of C57Bl/6J mice. This response was attenuated in $\alpha\beta^{-/-}$ mice but was significantly augmented in $\gamma\delta^{-/-}$ mice at all time points. 3) Studies using RNA arrays in purified T cells, respectively, reveal significant changes in many genes implicated in monocyte accumulation, epithelial cell growth, and T cell activation/accumulation. Of 1093 significantly changed genes in αβ or γδ T cells, 19 genes are up in both populations and 38 genes are down in both populations, 160 genes are up in γδ T cells and down in αβ T cells, 96 genes are up in αβ T cells and down in γδ T cells. Several significant (i.e., z score > 2.0) functional microarray pathway profiles (MAPPs) were revealed with MAPPFinder including biological pathways and functionally grouped genes that are important in peptide antigen binding, defense responses, regulation of protein metabolism, inflammatory responses, Th1 responses, response to pathogen, hematopoiesis, and lymphocyte differentiation.

Conclusions: These data indicate that 1) T cell activities contribute to macrophage accumulation and epithelial cell integrity in the lung following acrolein exposure, 2) αβ and γδ T cell populations represent distinct functional cell types in the lung and respond in a fundamentally distinct manner, and 3) global expression analyses of the whole lung and purified T cells will identify novel mediators controlling the pulmonary response to acrolein exposure.

Long-Term Effects of Traffic-Related Air Pollution on Respiratory and Cardiovascular Mortality (NLCS-AIR Study)

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Recent cohort studies suggested that long-term exposure to particulate matter air pollution, estimated mostly as city average concentrations, is associated with increased mortality. A recent (initial) study in the Netherlands found an association between local scale traffic related air pollution and mortality. We conduct a cohort study to evaluate the association between individual long-term exposure to traffic-related air pollution and mortality (NLCS-AIR study).

The NLCS-AIR study involves an existing cohort study on the relationship between diet and cancer (NLCS study), which started in 1986, with approximately 120,000 subjects aged 55-69 at enrollment (48.2% male) living in 204 communities spread all over the Netherlands. The exact home address of all participants in 1986, and in addition residential history after 1986, is known. The follow-up period is 1986-1996.As in the initial study, individual long-term exposure to NO_2, NO, Black Smoke, and SO_2 will be considered to be a function of a regional, urban, and local component. Exposure will be estimated based on the 1986 home addresses which were transformed into standard Dutch geographical coordinates; this was possible for ~ 98% of the addresses.

The regional component has been estimated by inverse distance weighed interpolation using air pollution measurements from regional background stations. The urban component has been assessed using address density and other land use variables in a regression model with residual urban concentrations measured at regional and urban stations as dependent variables. The local component has been estimated using a digital road network to which collected traffic intensity data have been linked. Two indicators for the local component were estimated using GIS: 1) traffic intensity on nearest road together with natural logarithm of distance to this road, and 2) sum of traffic intensity in a buffer of 100 m around each home address. Further, a quantitative estimate of the local component was estimated using a regression model with residual traffic concentrations as dependent variables and sum of traffic intensity in a 100 m buffer as predictor variable. This quantitative local estimate was added to the regional and urban background concentration. Overall regression models using both the regional, urban and local component predicted a large part of the variation in air pollution concentrations with explained variances of 83%, 46%, 59%, and 55% for NO_2, NO, Black Smoke and SO_2, respectively.

We are investigating the association between cause-specific mortality and long-term exposure to traffic-related air pollution using the case-cohort approach. Cases were enumerated from the entire cohort, whereas accumulated person-years for the entire cohort were estimated using a subcohort of ~5,000 participants. As data on age, gender and smoking were coded for the entire cohort, we are comparing results of a full cohort analysis, a sub-cohort analysis resembling our original work, and a case-cohort analysis to establish sensitivity of results to alternative analytic approaches.

Determination of Acrolein and Other Toxic Carbonyls in Air for Exposure Assessment

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Acrolein is considered one of the greatest non-cancer hazardous organic air pollutants. Current methods for determining acrolein typically employ adsorbent-filled cartridges containing derivatizations agent such as dinitrophenylhydrazine. However, these methods have limitations such as unstable derivatives, co-elution of similar compounds, and ozone interferences. Due to these problems, the currently available acrolein methodologies suffer from poor sensitivity, selectivity and reproducibility.

The objective of this research was to develop an analytical method to determine low part-per-trillion concentrations of acrolein and other volatile carbonyls in ambient air samples with short sampling times. The method uses a mist chamber to collect carbonyls by forming water-soluble carbonyl-bisulfite adducts that effectively trap the carbonyls in the solution. The mist chamber methodology proved effective with a collection efficiency of 70+% for each mist chamber. After the sample collection, the carbonyls are liberated from the bisulfite through the addition of hydrogen peroxide that converts the bisulfite to sulfate, which reverses the bisulfite addition reaction. The free carbonyls are derivatized by pentafluorohydroxlyamine, extracted in hexane and analyzed by gas chromatography mass spectrometry.

The analytical method was applied in a pilot experiment to determine acrolein concentrations at the Peace Bridge plaza in Buffalo, NY. Samples were collected upwind and downwind of the plaza every two hours from 7:00 am to 7:00 pm for three days in July 2005. In addition, XAD-2 adsorbent cartridges coated with 2-(hydroxymethyl)piperidine (OSHA method #52) and dansylhydrazine (DNSH) based passive samplers were deployed at the downwind site by the Spengler Research group to provide an inter-method comparison. The results showed that the Peace Bridge was clearly a source of acrolein, but the extent of enrichment was not as great as expected. The acrolein concentrations correlated with west-bound automobile traffic that was stopped by the toll plaza. The OSHA cartridges proved to be too insensitive to determine ambient acrolein concentrations. The DNSH passive samplers gave concentrations near the limit of detection for the method, hence the results were less consistent and the temporal trends were internally inconsistent. However, the overall results were similar, albeit a little higher, than the mist chamber results.

The method was then fully validated by determining atmospheric acrolein concentrations at three sites in Northern California reflecting hemispheric background, biogenic-dominated region, and an urban environment. The resulting acrolein concentrations were 0.056, 0.089, and 0.29 $\mu g/m^3$, respectively, which were all above the United States Environmental Protection Agency Reference Concentration of 0.02$\mu g/m^3$. The minimum detection limit for the method was 0.012 $\mu g/m^3$, which is below other published methods. Method consistency was good with relative standard deviations ranging from 19% at the hemispheric background site to 3% at the urban site. In addition, the absolute accuracy of the method was verified through the use of acrolein-d_4, which was added to each mist chamber solution prior to sample collection. Methacrolein, methyl vinyl ketone, crotonaldehyde, glyoxal, methyl glyoxal and benzaldehyde were also quantified at these three sites. With the exception of crotonaldehyde, all these carbonyls were higher in the urban site compared to the remote sites.

Diesel-Induced Venous Congestion and Vasoconstriction: A Potential Link to Heart Failure Symptoms

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Acute heart failure morbidity and mortality has been linked to daily air pollution concentrations. Heart failure patients admitted to hospitals typically report two symptoms/signs as primary complaints: dyspnea and elevated venous pressure. Given recent evidence of vascular constriction induced by air pollutants in both human and animal studies, we hypothesize that systemic venous constriction in the setting of profound cardiac limitation would promote venous congestion and symptoms of acute cardiac decompensation. To study this, we are conducting investigations 1) in isolated arteries and veins exposed to compounds common to combustion-source atmospheres and 2) in a hamster model of cardiomyopathy exposed by inhalation to diesel exhaust.

The isolated vessels (mesenteric arteries and veins) are harvested fresh from C57BL/6J mice and immediately placed in ice-cold physiologic saline. The vessels are then mounted between two micropipettes, warmed to 37°C and pressurized to physiological ranges. The vessels are continuously exposed via the supernatant to soluble components of whole diesel exhaust, then assayed for dose-response relationship to an endogenous constrictor (endothelin-1) and dilator (spermine nonoate, a nitric oxide donor). Early results suggest that acetaldehyde, but not acetone, enhances the constriction to endothelin and diminishes dilation to nitric oxide.

For whole-body studies, cardiomyopathic hamsters were obtained late in life and exhibited significant deficits in cardiac function (fractional shortening = 0.15-0.20; normal ~0.60). The hamsters were instrumented with radiotelemetry devices with pressure catheters placed in the thoracic vena cava. Thoracic venous pressure (Pven) was thus measured continuously throughout a control day and two exposure days. Exposures consisted of 3 x 1-hour exposures per day to 300 µg PM/m^3 whole diesel exhaust. While control (n=4) and exposed (n=5) groups were not statistically different on the control day (Pven ~ 5 mmHg in both groups), Pven increased dramatically (13 mmHg) on exposure days in the exposed hamsters, while controls exhibited no change. Furthermore, aortas isolated from a separate cohort of non-telemetered hamsters exposed to diesel for single 1-hour periods demonstrated significant increases in lucigenin-enhanced chemiluminescence, indicating elevated vascular oxidative stress cause by diesel exhaust.

Combined, these studies support the overall hypothesis that whole exhaust constituents may drive a venoconstrictive response that, in the setting of a severely impaired heart, leads to symptoms of congestion. Further research will be needed to confirm the roles of the various soluble organic air toxics found in combustion-source atmospheres.

Heterogeneity in Individual Airway And Immune Responses To Diesel Exhaust Suggests A Susceptible Subgroup

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The ability of diesel exhaust (DE) to enhance allergic and asthma responses has been suggested by epidemiological studies and murine asthma models. We have used a human DE inhalation model to determine whether the immunological and physiological changes observed in the upper airway also occur in the lower airways. Specifically we exposed human volunteers to diesel exhaust generated by an International 6.9 liter engine (Ford F250 diesel pickup truck which has 170 horsepower at 3000 rpm). Using this approach we performed a double-blind randomized cross-over controlled exposure to filtered air, diesel exhaust (100 $\mu g/m^3$) and nitrogen dioxide for two hours. We compared lung function and immunological responses (cell influx, allergic antibody, cytokine, chemokine and mediator production) in sputum derived from asthmatic vs. non-asthmatic subjects. Generation of DE was reproducible and representative of diesel exhaust in the "real-world" and was well tolerated by all subjects. For each exposure, diesel particle numbers were within 6% of our target goal of 100 $\mu g/m^{-3}$. DE exposure had no effect on respiratory or systemic measures in any of the healthy subjects studied. In contrast, there was a marked variability in response to DE (but not NO_2 or air) in our asthmatic group of subjects (Individuals who were >18 years of age, asthmatic with skin test sensitivity to at least one allergen). This variability was observed in symptom, respiratory, cellular and inflammatory cytokine responses. This heterogeneity to DE resulted in negative results when pooled analysis was performed. However, sub-group analysis showed that individuals in whom DE resulted in increased bronchial reactivity also demonstrated increased symptoms, increased cellular influx and increased IL-8 production.. Thus when we ranked 7 key independent markers of inflammation measured in response to DE we saw that 3 out of 10 asthmatic subjects had all seven parameters in the top 40^{th} percentile. Binomial distribution demonstrates that the probability of this occurring by chance is $P= 4.87 \times 10^{-7}$.Similar results were not observed in response to NO_2 or filtered air, or in the healthy subjects. We genotyped the subjects and saw that all three (100%) high responders had the GSTM1 *null* variant which we have previously established is a marker for increased susceptibility to PM. In contrast, only 3 out of the 7 (42%) poor responders were GSTM1 *null.* Why these 3 individuals did not respond to DE is unknown, possibly the responders had greater asthma severity, or possibly other genes played a role. We therefore conclude that there is a susceptible subgroup of asthmatic subjects with increased susceptibility to DE and that although asthma and GSTM1 null genotype are likely factors in determining responsiveness, other as yet undetermined factors also contribute.

Effect of Sequential Irish Bans on Coal Sales on Hospital Admissions

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Objectives: In 1990 the Irish Government banned the sale of coal within the city of Dublin, leading to an immediate drop of 70% in average particulate (Black Smoke) concentrations. Based on the Dublin experience, similar bans were put in place in Cork in 1995, in five other cities in 1998 (Limerick, Drogheda, Dundalk, Wexford, and Arklow), and in five more cities in 2000 (Galway, Waterford, Celbridge, Leixlip, and Naas). We have previously presented analyses of the effect of these sequential bans on air pollution levels and mortality rates. This poster presents analyses of hospital admissions.

Methods: We retrieved summary records of hospital admissions for cardiovascular (ICD9 390-459), respiratory (ICD9 390-459), digestive (ICD9 520-579), and fractures (ICD9 800-829) diagnoses for the hospitals serving the eleven study communities for the years 1993 through 2004 from the Economic and Social Research Institute based on the national Hospital In-Patient Enquiry (HIPE) admissions data reporting system. Air pollution, weather, and census data were compiled for the years 1990 through 2003. Directly standardized hospitalization rates for cardiovascular and respiratory admissions were calculated adjusted to the 1996 Irish population in sex-specific 5-year age classes. Influenza periods were identified as weeks in which % deaths in Ireland from influenza and pneumonia were above the 95th percentile of expected. Long-term trends in admissions were estimated based on age-standardized hospital admissions for fractures and digestive system disorders. We estimated the effect of the coal sale ban in each city on standardized cardiovascular and respiratory hospital admission rates, adjusting for weather, respiratory epidemics, and long term trends in the reference admissions (digestive system and fractures).

Results: The sequential ban on coal sales in 1995, 1998, and 2000 in Ireland led to immediate reductions in average Black Smoke concentrations, particularly in the heating season. Preliminary analyses suggest reductions in cardiovascular and/or respiratory hospital admissions were detectable in some of the communities following the imposition of the ban on coal sales. However, these data show indications of other temporal patterns such as intensity of the influenza epidemics, trends in population risk factors, changes in medical practice, completeness of reporting, discharge diagnosis coding, and hospital referral and admissions practices which require further study.

Characterization of Primary and Secondary Particles and Associated Personal Exposures Near a Major International Trade Bridge Between the U.S. and Canada

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The primary objective of this study is to determine whether residents who live immediately and further downwind of the Peace Bridge Plaza Complex (PBC), located in Buffalo, New York, are exposed to greater levels of direct emissions from its truck traffic or other upwind or indoor sources. The study is designed to facilitate a subsequent full-scale health effects study.

Both summer and winter field intensives were conducted to address seasonal variations in pollutant concentrations, residential ventilation, and human activity patterns. A combination of integrated and semi-continuous particle monitors were used to conduct upwind and downwind stationary monitoring; mobile monitoring; indoor, outdoor, personal monitoring at 10 residences in a northeast trajectory from the PBC; and indoor/outdoor monitoring at an additional residence close to the PBC.

The findings indicate that air traveling over the truck and toll plaza substantially increased the concentration of particle number, at proximities to within 500 meters, and to a lesser extent black carbon, while regional upwind sources contributed to at least 50% of PM2.5. In general, upwind PM measurements were relatively consistent, by particle number (~10,000 p/cc), size (40 – 150 nm), and PM2.5 mass (15 – 20 $\mu g/m^3$). Depending on the location of the mobile lab and time of day, local sources tended to contribute to the overall temporal and spatial patterns, but clear separation of nearby and distant sources were observed. A Lagrangian particle tracking model for evaluating the transport and dispersion of vehicular emissions from the PBC was developed to improve estimation of ultrafine particle number concentrations in the west side neighborhood. Results show that the predicted concentrations downwind are within 5% of the measured, except for a 2 fold over-prediction for 16 nm particles at one of two sites.

Outdoor PM2.5 concentrations at the homes that were monitored did not decrease with distance from the PBC. This finding is consistent with the relatively small contribution of the PBC to PM2.5, and is an indication of the importance of other local sources. However, OC/EC ratios immediately downwind of the PBC tended to be lower than those upwind at the GLC or further downwind at the homes, which supports the higher contribution of fresh vehicle emissions to PM2.5 closer to the PBC. Consistent with previous human exposure studies (Wallace, 1996), indoor and personal ultrafine particle counts and PM2.5 concentrations were, in general, higher than outdoor concentrations due to indoor sources. When there were no obvious indoor sources, the ultrafine and fine particle concentration indoors was lower and less variable than the outdoor concentration, demonstrating the attenuation of particles as they infiltrate indoors.

The results of the pilot study indicate that residents living close to PBC have higher exposures to the particulate components emitted from the associated traffic, which may contribute to the high asthma incidence in the area. Indoor and other local sources also substantially contribute to particle exposures. A full-scale study is required to determine whether exposures and health outcomes are directly associated with emissions from the diesel-emitting traffic of the PBC.

Assessing Exposure to Air Toxics in Microenvironments Dominated by Mobile Sources

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The Desert Research Institute conducted field measurements in California's South Coast Air Basin during summer 2004 and winter 2004/5 of volatile air toxics, PM2.5 mass, black carbon and polycyclic organic matter (POM) to characterize and assess exposures to air toxics in microenvironments dominated by mobile sources. These exposure measurements are being compared to the annual and seasonal average concentrations derived from MATES–III, which is being conducted by the South Coast Air Quality Management District (SCAQMD) from February 2004 to March 2006. Our study focuses on two specific exposed populations – 1) in-cabin exposure of commuters traveling by automobile and 2) residents living near major roadways. In-cabin measurements were made along three freeway routes in the western and central SoCAB during the morning commute period and along truck routes later in the morning. Residential exposures were measured at three locations with varying proportions of diesel and gasoline vehicle traffic. The time-integrated methods included: pumped whole-air canister samples (with upstream NOx denuder) for benzene, toluene, ethylbenzene, xylenes, styrene, 1,3 butadiene, MTBE and n-hexane; 2,4-dinitrophenylhydrazine (DNPH) cartridges for acrolein, formaldehyde and acetaldehyde; Teflon filters for gravimetric mass, quartz filters for organic and elemental carbon (IMPROVE protocol); Teflon-impregnated glass fiber filters with backup XAD resin for speciated particulate and semi-volatile organic compounds. Continuous methods include: both an active non-dispersive infrared (NDIR) and a passive electrochemical cell device for CO; NDIR for CO2; chemiluminescence analyzer for NO and NOx; nephelometer for PM2.5 mass, photoacoustic analyzer for black carbon; an active photo-ionization detector (PID) for volatile organic compounds; and optical particle counter for particle size distribution. The continuous measurements were also used to characterize the gradients in pollutant concentration from the residential sampling sites to nearby roadways and MATES regional and microscale sites.

This presentation summarizes the results from the summer and winter field studies. The ranges in observed in-cabin and near-roadway residential exposures are compared to the annual averages from the local air toxics and PM monitoring programs. The microenvironment/ambient ratios will be compared to the default values that are used in exposure models. We also characterize and estimate contributions of gasoline- and diesel-powered vehicles to exposures to gaseous air toxics and carbonaceous particulate matter in various vehicle-dominated hotspots in the SoCAB using chemical mass balance and multivariate analysis approaches.

Disparate Allergic Airway Responses to Diesel Exhaust Inhalation During Allergen Sensitization Versus Allergen Challenge

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Diesel engine exhaust (DEE) contributes to air pollution, and has been studied as a potential contributor to allergic responses in laboratory animals and humans. We compared the allergic respose of rodents exposed to DEE in two allergic models; one focused on allergen sensitization and one on allergen challenge. Brown Norway rats were sensitized to ovalbumin (OVA) with 3 daily intranasal instillations of 0 or 0.5% OVA, and then challenged with IN OVA or saline vehicle 14 days later. Rats were exposed to DEE diluted to 30 or 300 micro-g/m^3 particulate matter or clean air as a control during either sensitization or challenge to OVA. All rats were sacrificed 24h after the last OVA challenge, bronchoalveolar lavage fluid (BALF) was collected and analyzed for cellularity and secreted mucins, and lungs were processed for routine morphology and histochemical analysis of intraepithelial mucosubstances (IM). OVA sensitization and challenge caused increased total inflammatory cells, neutrophils, eosinophils, and mucin glycoprotein 5AC in BALF, and IM in proximal (2-fold increase) and distal (10-fold) pulmonary axial airways. The lowest DEE exposure during OVA sensitization enhanced OVA-induced BALF cellularity by 1.6-fold, mostly due to an increase in neutrophils. By contrast, exposure to this same exposure level during OVA challenge resulted in an attenuated OVA-induced BALF total cells, neutrophils and eosinophils by 50%. Exposure to the high DEE exposure level had no effect on OVA-induced changes in BALF cellularity or mucin secretion. OVA-induced increases in IM were unaltered by DEE exposure during allergen sensitization, but both DEE exposure levels during allergen challenge inhibited OVA-induced increases in IM in distal airways by 50%. These data demonstrate that inhalation exposure to DEE can both inhibit and enhance allergic airway inflammation and mucus production. Modulation of these responses is dependent on the time of DEE exposure during the development of allergic disease. (Supported by the Health Effects Institute 03-8)

Measurement and Modeling of Exposure to Air Toxic Concentrations for Health Effect Studies and Verification by Biomarker (MATCH Project)

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OBJECTIVES To quantify the magnitude and range of individual personal exposures to a range of air toxics and to develop models for exposure prediction based upon time/activity diaries.

Specific Goals of Research
1. To use personal monitoring of non-smoking volunteer subjects with a range of residential locations and exposure to non-traffic sources to assess daily exposures. **2.** To determine microenvironment concentrations of a range of air toxic substances (VOC hydrocarbons including 1,3-Butadiene and polycyclic aromatic hydrocarbons) taking account of spatial and temporal variations and hotspots. **3.** To optimise a model of personal exposures based upon microenvironment concentration data and time/activity diaries and to intercompare modelled exposures with exposures independently estimated from personal monitoring data. **4.** To produce a scheme for categorising exposure (by compound) according to location of residence and other lifestyle and exposure factors (e.g. ETS) for use in design of case control and ecological studies of cancer incidence.

METHODS *Personal Exposure Measurements* Using actively pumped personal sampler enclosed in a briefcase, volunteers with a range of exposure patterns collect 24-hour integrated personal samples during 5 days. *Microenvironment Sampling* During the period when personal exposures are being measured, there is a simultaneous programme of measurement of workplace and home environment concentrations of the same air toxics. These measurements also include trafficked roadside locations, parks, cars, buses, trains, cinemas, pubs, restaurants, libraries, garages, train stations. *Personal Exposure Modelling* Volunteers are asked to list in an activity diary their activities each day, to describe the places they visit and the journeys they take. With this information it will be possible to reconstruct exposures to air toxics based upon the location information and time activity records.

ANALYSIS VOC collected in tubes packed with Tenax GR and Carbotrap and 1,3-butadiene tubes packed with Carbopack B and Carbosieve SIII are analysed by means of a thermal desorber interfaced with a GC/MS. Particle phase PAH collected onto a glass fibre filter are extracted with solvent, purified and concentrate prior to been analysed into a GC/MS. Nicotine and cotinine are **s**imultaneous extracted and analysed using also a GC/MS.

SUMMARY OF RESULTS The variability of personal exposure concentrations mainly reflects the range of activities the subjects engaged in during the 5-day period of sampling, as well as the variability in ambient and indoor levels, which is due to varying environmental conditions. Concentrations were generally within the expected range of values and remained consistently higher during days of the week associated with increased vehicle use and ETS exposure. In most cases "home day" concentrations were higher than "home night" concentrations for the same subject. Although a limited amount of micro-environmental data have been analysed, it appears that personal exposure levels are in reasonable agreement with "home" and "work" concentrations.

INTERPRETATION AND CONCLUSION The initial results from the sampling campaign have shown personal exposure patterns that are consistent with the associated micro-environmental concentrations and subject lifestyles.

A Time-Series Study of Ambient Air Pollution and Daily Mortality in Shanghai, China

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A time-series study to evaluate the association between mortality outcomes (both total and cause-specific) and major air pollutants (PM_{10}, SO_2, NO_2 and ozone) is being conducted in the urban area of Shanghai, using 4 years of daily data (2001-2004). Up to date, the collection, validation and auditing of all the air pollution, weather and mortality data have been completed, and preliminary data analysis has been performed using the Common Protocol of PAPA project. The results showed that from 2001 to 2004, the average daily mean concentrations of PM_{10}, SO_2, NO_2 and ozone were 102.0, 44.7, 66.6 and 63.3 $\mu g/m^3$ respectively. At meantime, the average daily mean temperature, relative humidity and dew point temperature were 17.7°C, 72.9% and 12.4°C. A total of 173,911 non-accidental deaths were recorded in the urban area of Shanghai from 2001 to 2004. On average, there were 119 deaths per day, among which approximately 44 persons died from cardiovascular diseases, 14 from respiratory diseases, and 29 from cancer. Generalized additive model (GAM) with natural and penalized spline models was used to analyze the mortality, air pollution, and covariates data. As a result of the preliminary analysis, the air pollution (PM_{10}/SO_2/NO_2/ozone) levels in Shanghai from 2001 to 2004 were significantly associated with mortality from all causes and from cardiopulmonary diseases. In the single-pollutant models, an increase of $10\mu g/m^3$ of two-day moving average of PM_{10}, SO_2, NO_2 and ozone corresponds to 0.30% (95%CI 0.18%-0.41%), 1.00% (95%CI 0.65%-1.34%), 1.07% (95%CI 0.75%-1.38%), and 0.46% (95%CI 0.17%-0.75%) increase of all-cause mortality, respectively. The mortality risk of elderly people (> 65 yrs) showed a stronger association with air pollution than that of younger people. Sensitivity analyses showed that the results were generally insensitive to model specification and the type of spline model used. Generally, the regression coefficients found in Shanghai are lower than those estimated in developed countries. As a study sponsored by HEI PAPA program, the results of this project are expected to supplement key scientific information on air pollution-related health effects in Shanghai, thereby providing local decision-makers with information needed to set prioritized air pollution control measures with greater health benefits.

Congestion Charging Scheme in London: Assessing its Impact on Air Quality

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The Congestion Charging Scheme (CCS) was introduced on 17th February 2003 with the aim of reducing the number of cars entering central London, while increasing public transport availability. Vehicle owners pay a charge of £5.00 (£8.00 since July 2005) to enter central London between 7:00 am and 6:30 pm during the working week. To take advantage of this traffic management scheme this HEI-sponsored study has two main objectives:

1. To develop an analytical framework for assessing ambient air quality data within and outside the CCS zone on order to determine the impact of this traffic management scheme on air quality in London.
2. To examine the oxidative properties of ambient PM_{10} in London to ascertain whether the implementation of the CCS resulted in a change in its oxidative activity.

The CCS project has been running for 15 months with good progress achieved.

In work package 1, (a) The CCS database has been created and populated with ratified 15 minute mean pollutant, meteorological and traffic data for the time period 17th February 2001 to 16th February 2005. The database contains over 14 million pollutant data points; (b) SQL data mining queries have been written to summarise data in a range of formats for input into statistical analysis software; (c) The CUSUM statistical method has been researched and its suitability assessed for application to time series pollution data. CUSUM has been used to screen the CCS database over the four year period 17th February 2001 to 16th February 2005; (d) Work has begun on analysis of the CCS air pollution measurements using time-series methods; (e) We have updated and verified the tools needed to undertake detailed comparative emissions scenarios for the CCS zone and surrounding areas.

In work package 2, (a) PM filters have been retrieved from the Government archive and a database established holding information on the duration of filter collections and the collected mass; (b) Protocols have been established for the extraction of PM from these filters. To date, we have extracted PM from 457 filters. Of these, 410 samples have been tested in our oxidative stress screening system; (c) Work has begun on identifying and obtaining filters from the proposed CCS extension zone. These filters will be used to establish the baseline oxidative potential data for this area prior to it becoming part of the zone in February 2007; (d) We have installed and commissioned an additional FDMS sampler and from July 2005 filters from this site and another have been utilised to address the contribution of PM organic components to PM oxidative potential.

The London Low Emission Zone Baseline Study

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Road traffic is a major contributor to air pollution in London and action is needed to address road transport emissions. The London Congestion Charging Scheme has reduced vehicle numbers and increased vehicle speed, however the area over which these changes have occurred is small. The introduction of the London Low Emission Zone (LEZ) in 2008 in contrast, aims to tackle vehicle emissions by restricting the entry of the oldest and most polluting vehicles across all of greater London, an area of 2644 km^2 in which more than 8 million people reside. Given the magnitude and nature of the proposed LEZ intervention there is good reason to believe that it will lead to a range of health benefits for London residents.

The LEZ baseline study has four main objectives:

1. To produce model predictions of the effects of the LEZ (PM_{10}, NO_2) based upon the Greater London Authorities preferred scenario and to estimate the areas in London that show the greatest change in atmospheric concentration and population exposure.
2. To design a comprehensive LEZ impacts monitoring network to provide robust datasets for assessing the air pollution concentrations, before and after the implementation of the LEZ.
3. To examine the oxidative properties of ambient PM_{10} across greater London to ascertain whether implementation of the Low Emission Zone (LEZ) results in a change in its oxidative activity.
4. To develop procedures and methodology to extract a wide range of general health indicators from the primary care doctor network to facilitate future health-based studies.

The project started in December 2005. Objective 1 has been completed while Objectives 2-4 are being implemented. Under Objective 2, five monitoring sites identified to be in key positions have been upgraded while a completely new monitoring station has been established in Tower Hamlets at an important road location. In Objective 3, the supply of both PM_{10} filters from the designated monitoring sites has been established and staff are being trained to assess the oxidative potential of these PM samples. Given the updates to the monitoring network plans are now in place to also examine $PM_{2.5}$ oxidative activity. In Objective 4, work is underway to recruit key primary care health units.

Nanotoxicology of Fine PM

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A multitude of factors may influence the pathogenicity of airborne particles including particulate size, load, surface area and chemistry. However, little is known about the interaction of ambient particulate with lung lining fluid constituents, into which depositing particles are incorporated. Since the coating of deposited particulate by host proteins may modulate their biological activity, studies of such interactions will provide new information as to how inhaled pollutants may induce pulmonary and cardiovascular toxicity.

This two year project builds on previous studies led by the Principal Investigator (PI) which showed that in contact with lung lavage fluid, certain surface species were desorbed from—and protein/lipid signature molecules were adsorbed to—$PM_{2.5}$ surfaces. Furthermore, published studies of the behavior of model particle and protein mixtures *in vitro* showed that particles exposed to certain lung surfactant proteins and lipids adsorbed the molecules, changing particle behaviors and subsequent exposure responses in cell models. The new project combines the disciplines of nanotechnology, proteomics and *in vitro* cell testing to study the interaction of PM surfaces with selected lung lining fluid components. The study objectives are to (1) determine $PM_{2.5}$–lung lining liquid interactions and (2) determine the clinical significance of PM–lung opsonin interactions in PM health effects (3) offer a plausible explanation for underlying susceptibility of subpopulations exposed to fine particles.

The project focuses on lung surfactant and surfactant-associated opsonins. Previously gathered time-of-flight secondary ion mass spectrometry (ToF-SIMS) data was analyzed in detail to identify the proteins and or lipids responsible for the signatures detected at $PM_{2.5}$ surfaces in previous studies. Factor analysis isolated and positively identified surfactant and specific proteins signatures on $PM_{2.5}$ surfaces treated with lung lining fluid. Measurements of different sized and functionalized particles suspended in broncho-alveolar component solutions were made using a Zetasizer (Malvern Instruments) during a three month experimental visit to Birmingham University, UK. Surface charge and particle size distribution measurements showed that particle size, surface charge and agglomeration behavior significantly changed in the presence of different lung proteins. Protein-surface interactions of similar materials were further quantified using atomic force microscopy (AFM) at Birmingham University. These measurements facilitate further quantification of the specific molecular interactions between particles of varying characteristics and lung opsonins. AFM was able to discern molecular scale differences in surface-liquid interactions in different lung liquid component and surface systems.

In Year 2 (November 2005), data gathered during the UK visit will be processed. Finally, epithelial (A549) and alveolar macrophage (AM) cell lines will be tested to assess the clinical significance of the earlier findings. Overall, the study results are expected to inform PM-related cardio-respiratory disease research and public health policy. This research study addresses key HEI research priorities.

Induction of Vascular Endothelial Inflammatory Response by Metal Oxide Nanoparticles

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Objectives: Exposure to particulate matter in ambient air correlates with increased cardiovascular mortality. Because inflammation-induced vascular endothelial dysfunction is implicated in atherosclerosis and acute coronary disease, we tested the hypotheses that exposure of endothelial cells to nanoparticles elicits an inflammatory response and that the composition of the particles is relevant.

Methods: Cultured human aortic endothelial cells (HAECs) were exposed for 2-8 hrs to three different types of environmentally relevant metal oxide nanoparticles (all with a mean diameter less than 100 nm): yttrium oxide (Y_2O_3), iron oxide (Fe_2O_3) and zinc oxide (ZnO) at concentrations of 0.001-50 μg/ml. Real-time RT-PCR was used to determine mRNA levels of the three pro-inflammatory markers intracellular cell adhesion molecule-1 (ICAM-1), interleukin-8 (IL-8), and monocyte chemotactic protein-1 (MCP-1). Protein levels of the three inflammatory markers were determined using either Western blotting or ELISA. Nanoparticle-HAECs interactions were studied using inductively coupled plasma mass spectrometry (ICP-MS) and transmission electron microscopy (TEM).

Results: The ICP-MS data demonstrated that nanoparticle delivery to the HAEC surface and uptake within the cells correlates directly with particle concentration in the cell culture medium. The TEM data revealed that all three types of nanoparticles are internalized into HAECs; however, while Fe_2O_3 and Y_2O_3 particles are found primarily within intracellular vesicles, ZnO particles often localize near the cell membrane. The real time RT-PCR results demonstrated that Y_2O_3 and ZnO nanoparticles increase mRNA levels of the three inflammatory markers in a dose-dependent manner. At the highest concentration tested (50 μg/ml), a 4-hr exposure to Y_2O_3 nanoparticles increased HAEC MCP-1, ICAM-1, and IL-8 mRNA levels 6-, 5-, and 3-fold relative to control cells. A more modest increase was observed at an Y_2O_3 nanoparticle concentration of 10 μg/ml, while lower concentrations failed to provoke an inflammatory response. ZnO nanoparticles not only elicited a dose-dependent inflammatory response but also led to dose-dependent cellular toxicity. At 50 μg/ml, a 4-hr exposure to ZnO nanoparticles increased MCP-1, ICAM-1, and IL-8 mRNA expression by 11, 13, and 7 times respectively. Interestingly, Fe_2O_3 nanoparticles did not induce an inflammatory response at any of the concentrations tested and resulted in no visible cell toxicity. To investigate the time dependence of nanoparticle-induced changes in mRNA expression, we tested additional time points of 2 and 8 hrs. The data show that the mRNA up-regulation induced by ZnO nanoparticles is also present at both the 2- and 8-hr time points. On the other hand, the inflammatory response induced by Y_2O_3 nanoparticles is absent at the 2-hr time point but is present at 8 hrs. ELISA and Western blot analysis confirmed that the increase in mRNA levels is followed by an increase in protein concentrations.

Conclusions: Our results demonstrate that metal oxide nanoparticles induce inflammation in vascular endothelial cells but that the magnitude of the response and its dynamics depend on particle composition.

Particulate Air Pollution and Mortality in New York City

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OBJECTIVES The American Cancer Society (ACS) study of air pollution and mortality has supplied important evidence on the health effects of chronic exposure to fine particulate air pollution (PM2.5). Recently, Jerrett et al. (2005) found in Los Angeles (LA) a near tripling of the relative risk (RR) of mortality compared to the earlier Pope et al. (2002) study based on between-city exposure gradients.

In this study we pursued two objectives: (1) to derive estimates of ambient concentrations of PM2.5 in another large metropolitan area containing sufficient ACS data to support statistical inference (i.e., New York City); and (2) to test statistical associations between PM2.5 concentrations and mortality in the ACS data set.

METHODS Health and Covariate Adjustment Data: Health data were extracted from the ACS Cancer Prevention II survey for 762 zip-code areas in the New York City (NYC) region. In total, 43,930 subjects lived in these zip codes (10,525 deaths during the follow up from 1982 to 2000). Exactly the same 44 individual confounders identified in earlier ACS studies of air pollution health effects were included (Pope et al. 2002).

Exposure Assessment: We developed regression equations to predict PM2.5 concentrations from air monitoring locations in the NYC region using proximate traffic, population, and land use data. Three year averages of (1999-2001) were calculated using daily data from the U.S. EPA's Air Quality Subsystem for 62 sites.

Health Effects Model: A multilevel Cox model was used to assess the air pollution-mortality association (Ma et al. 2003).

RESULTS Exposure Model: The final land use regression model predicts 66% of the variation in PM2.5 with three variables (traffic within 500 m, population within 1000 m, and industrial land use within 300 m of the monitors). This model estimates fine particulate matter concentrations at 13 validation locations to within 0.93 $\mu g/m^3$ (6.5% of actual concentrations).

Health Model: Ischemic heart disease (IHD) had a significant positive association with mortality. The IHD results were robust to control for 44 individual variables, to unemployment at the zip code level, and for clustering in the random effects.

Evaluated across the winter 10-90% exposure contrast of 3.9 $\mu g/m^3$ for the three-year average, the RR for ischemic heart disease is 1.20 (95% CI: 1.11-1.20). Although these RRs appear smaller than those reported for LA, the more limited range of exposure in NYC accounts for this difference. Using the same 10 $\mu g/m^3$ exposure contrast as the LA study, the significant RRs are even larger in NYC. Neither all cause nor other cause-specific deaths had a positive, significant association with PM2.5 in this population.

INTERPRETATION Unlike the LA results, in NYC we did not observe elevated mortality for all cause, cardiopulmonary, and lung cancer deaths. A positive urban-rural exposure contrast and opposite pattern in residual mortality complicates assessment of the relation between PM2.5 and mortality in NYC. The effect on IHD mortality, however, provide evidence of a specific association with high biologic plausibility that still finds expression against broader gradients of mortality and exposure.

Time Series Study of Air pollutants and Mortality in Ludhiana City, India

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Daily level of air pollutants, metrological parameters and mortality is being obtained in Ludhiana city of northern India for year 2002-2004. Data for RSPM, SO_2, and NO_x and temperature, relative humidity and wind speed has been obtained from 2002-2004. Daily mortality data has been collected for year 2004, and mortality data will also be obtained soon for year 2002 and 2003. Preliminary analysis of year 2004 revealed RSPM, SO_2, and NO_x level to be 320.7 (SD 116.5), 23.8 (SD 5.7), 61.3 (16.2) $\mu g/m^3$ at monitoring site I, 186.6 (SD 60.7), 15.4 (SD 3.2), 32.1 (SD 5.2) at site III, and 258.1 (SD 94.4), 20.4 (SD 5.2), 37.5 (SD 6.4) at site IV respectively. Monitoring station I & III record data on Monday, Wednesday and Friday whereas air pollution is monitored on Tuesday, Thursday and Saturday at station IV. The correlation of air pollutants between different monitoring stations and between pollutants in the same monitoring station was poor. All the pollutants were higher in winter months in all the monitoring stations. Temperature and relative humidity also varied a lot during the year. During 2004, a total of 9110 deaths had occurred with a daily mean of 25 (SD 6.15) and range of 9 to 48. Numbers of deaths are higher during winter months when air pollution level is also higher. R package will be used to fit GAM model to study the association of air pollutants with natural causes of mortality after taking into consideration temperature, relative humidity, and the days of the week. Sensitivity analysis will be conducted by fitting the model with 4-7 degrees of freedom and after taking into account the variability between different monitoring stations. A combined analysis with other cities in PAPA study will also be attempted.

Using Geographic Information Systems and Questionnaire Data to Predict Indoor and Outdoor Concentrations of Traffic-Related Air Pollution

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Air pollution exposure patterns, related to proximity to traffic as well as indoor sources and ventilation, may contribute to known spatial patterning of asthma morbidity. Incorporating such exposure patterns into large cohort studies requires models linking measured concentrations with available information. While studies have evaluated the relationship between traffic and outdoor concentrations, few have considered these relationships in residential settings or addressed indoor exposure patterns among high-risk individuals.

As part of the Asthma Coalition on Community, Environment and Social Stress (ACCESS) study, a prospective birth cohort assessing the contributions of environmental, social, and genetic factors to asthma etiology in urban Boston, we collected indoor and outdoor 3-4 day samples of nitrogen dioxide (NO_2) and fine particulate matter ($PM_{2.5}$) in 43 residences in summer and winter from 2003 – 2005. Reflectance analysis and X-ray fluorescence spectroscopy were performed on particle filters to determine elemental carbon (EC) and trace element concentrations, respectively. Homes were chosen based on neighborhood of residence and traffic density scores and consisted almost entirely of multi-unit residences.

To predict concentrations, we developed multiple indicators in GIS using data on traffic volume, roadway length, and proximity of homes to various road types. We additionally considered meteorological or site data that could modify the effect of traffic. Information on housing and behavioral characteristics was collected via standardized questionnaire. Ambient monitoring data were gathered from a central-site monitor.

Outdoor $PM_{2.5}$ was highly correlated with the ambient monitor, indicating relatively less spatial heterogeneity, with lower correlations for outdoor EC and NO_2. The ambient monitor was significant in all regression models. In addition, log($PM_{2.5}$) was significantly associated with total roadway length within 100 meters of the home, other nearby combustion sources, and population density ($R^2 = 0.76$). Log(EC) was predicted by roadway length within 200 meters, an interaction of roadway length and hours of still winds, and season ($R^2 = 0.43$). NO_2 was significantly associated with roadway length within 50 meters, modified by presence of an obstruction between the monitor and nearest major road, as well as season and population density ($R^2 = 0.56$).

Indoor concentrations were more strongly predicted by outdoor concentrations for pollutants without significant indoor sources, such as EC and sulfur, as expected. Weaker associations were shown for $PM_{2.5}$ and NO_2. For NO_2 and many particle constituents, terms such as cooking time, gas stove usage, or occupant density were significant predictors. Usage of sulfur indoor-outdoor ratios as a proxy for particle infiltration factors further increased the predictive power for multiple constituents.

We conclude that outdoor $PM_{2.5}$ displays more temporal than spatial heterogeneity and that indoor sources significantly influence indoor $PM_{2.5}$. In contrast, outdoor EC displays significant spatial heterogeneity related to proximity to traffic, with no indoor sources influencing indoor EC. Outdoor NO_2 is related to traffic but weakly associated with indoor NO_2, which is associated with gas stove usage. Exposure patterns for these three potential causative agents may therefore differ within our cohort, and future epidemiological studies should incorporate proximity to traffic and indoor pollution sources to minimize exposure misclassification.

Ambient and Personal Exposures to Air Toxics in Camden, NJ

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Numerous local stationary facilities (26 industrial/manufacturing) and mobile sources (150,000-260,000 truck trips/year) are located in or near the Waterfront South (WFS) neighborhood in Camden, NJ. To evaluate the impact of these sources on neighborhood air quality and personal exposures to air toxics, measurements of ambient and personal levels of air toxics in the WFS and Copewood/Davis Streets (CDS) neighborhood, an urban reference site located ~2 miles northeast of the WFS, and the MENTOR-1A source-to-dose modeling application will be performed in the 3-year project.

Over the past 2 years, personal (80 subjects) and ambient samples, including $PM_{2.5}$, VOCs, carbonyls, and PAHs, have been simultaneously collected for 24 hours in both neighborhoods on one weekday and one weekend during summer and winter, with a total of 64 sampling days. Given the intensity of local emission sources of air toxics in WFS, three "saturation sampling campaigns" were conducted for a duration of 24 or 48 hours at 38 evenly distributed sampling sites (22 sites in WFS and 16 sites in CDS) examining the spatial variation of VOCs and carbonyls.

High formaldehyde concentrations were observed at a fixed monitoring site in both WFS (58 $\mu g/m^3$) and CDS (58 $\mu g/m^3$), but higher formaldehyde concentrations were found in the WFS (56-160 $\mu g/m^3$) than in the CDS (44 – 146 $\mu g/m^3$) in the spatial variation study, suggesting major sources of formaldehyde located near WFS and a large impact on air quality in both neighborhoods. Specific pollutant levels (median and range) in WFS, such as $PM_{2.5}$ (28.5, 9.4-55.8 $\mu g/m^3$), toluene (2.52, 0.21-11.4 $\mu g/m^3$), BaP (0.61, non-detect to 2.04 ng/m^3), and acrolein (4.18, 1.0-6.9 $\mu g/m^3$), were found higher than in the CDS, where $PM_{2.5,}$ toluene, BaP and acrolein were 22.7 (4.2-70.3) $\mu g/m^3$, 1.92 (0.49-8.30) $\mu g/m^3$, 0.24 (non-detect to 0.93) ng/m^3, and 1.94 (0.3-10.2) $\mu g/m^3$, respectively. Based on the spatial variation study high concentrations of air toxics were found in areas close to the local emission sources in WFS. 200 $\mu g/m^3$ of toluene was observed at a site close to a mineral factory, 50.6 $\mu g/m^3$ MTBE at a site next to an automobile recycling facility; and 52.9 $\mu g/m^3$ xylenes at a site close to a power plant. These results validated our hypothesis that WFS is a "hotspot" for air toxics. A temporal variation was observed between weekdays and weekends. For instance, $PM_{2.5}$ concentration was higher on weekdays (median: 29.2 $\mu g/m^3$, range: 4.2-237 $\mu g/m^3$) than on weekends (median: 24.3 $\mu g/m^3$, range: 10-150 $\mu g/m^3$). This difference can be attributed to heavier traffic and active industrial operations on weekdays. Personal exposures to $PM_{2.5}$ (median level of 52 $\mu g/m^3$) and carbonyls (64 $\mu g/m^3$ for formaldehyde) were found higher in this study than those reported in other studies (e.g. 30.8 $\mu g/m^3$ for $PM_{2.5}$ and 20.5 $\mu g/m^3$ for formaldehyde reported in RIOPA study). We will continue acquiring to data solidify our current observations. Correlations between ambient and personal air toxic concentrations as well as exposure modeling will be conducted to assess the impact of local industrial and mobile sources on personal exposure and neighborhood air pollution.

* Assessing Children's Exposures to Diesel Exhaust from Commuting by Diesel School Buses Before and After Diesel Engine Retrofit

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Each weekday, 24 million American children commute to and from school by bus, where they may be exposed to elevated levels of diesel exhaust (DE). DE can affect children's respiratory health, resulting in inflammation of the lung's airways and worsening of asthma symptoms. Until this study, there have been no studies that relate diesel exhaust levels on school buses to the health impacts in student passengers. Despite our current understanding of diesel exhaust levels in school buses, it is unclear if retrofit technologies and different diesel fuel types will reduce levels of diesel exhaust and improve respiratory health. The ongoing retrofitting of diesel school bus fleets in the Seattle area school districts provides a framework to characterize diesel exhaust exposures and assess health outcomes in children before and after the retrofit, including diesel oxidation catalysts (DOCs), diesel particulate filters (DPFs), and closed crankcase ventilation (CCV). This 5-year longitudinal study quantifies the levels of on-bus DE exposure and respiratory health for all subjects over a 3-year monitoring period. Three exposure groups of school children (grades 1-5) are recruited from the Seattle and Tahoma school districts: 50 children riding cars, 150 children riding old buses that later become retrofitted, and 200 children riding buses that undergo several retrofitting processes. Monthly measures of pulmonary function using spirometry, pulmonary inflammation via exhaled nitric oxide, asthma symptoms, medications, and clinical encounters, are obtained on all children during the school year. Up to 100 study participants and their buses are monitored for ultrafine PM (using real-time P-TRAK), $PM_{2.5}$ (real-time active personal DataRam (pDR)), trace elements (XRF), particle-bound PAHs (real-time EcoChem), EC/OC (TOT), and NO_2 (active TEA tube). Source apportionment analyses and a lead-vehicle approach are conducted to distinguish children's exposure to DE from other on-road sources and to develop an exposure model for individual exposure estimates. This paper provides our pilot study results, discusses study design issues in relating reductions in diesel emissions directly to reductions in exposures and health effects, and gives a brief account of the preliminary results.

* Study not funded by HEI.

*** Associations Between Air Pollutants and Asthma Exacerbations in New York City**

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We sought to evaluate temporal associations between a panel of air contaminants and asthma emergency department (ED) visits in communities in the Bronx and Manhattan in New York City (NYC). Time-series analysis was used to determine whether and to what extent various air contaminants were associated with acute asthma exacerbations and whether the magnitude of the air pollution effect differed in the two communities. Air pollutant data were collected over approximately a two year period from January 1999 through November 2000 at centrally-located measurement stations in each community sampling a broad range of contaminants including ozone, sulfur and nitrogen oxides, particulate matter ($PM_{2.5}$ and PM_{10}), acidic and basic gases, carbonyl compounds and bioaerosols. Samples for $PM_{2.5}$ components including sulfate, elemental and organic carbon and metals were also collected. ED data on asthma visits for the corresponding dates were collected from the 22 hospitals throughout NYC that served the communities surrounding the air monitoring stations. From each hospital, data for patients who lived in zip code areas within approximately 1.5 miles of either measurement site were extracted. We used Poisson regression to test for effects of 14 key air contaminants on daily ED visits, with control for temporal cycles, temperature, and day of week effects. The core analysis utilized the average exposure for 0-4 day lags. Sensitivity analyses examined individual lag effects.

Concentrations of air contaminants were generally similar in the two communities, with mean levels tending to be slightly higher in Manhattan in most cases. Mean ozone and total pollen levels were significantly higher in the Bronx, compared to Manhattan. In single-pollutant models, five of 14 key pollutants had statistically significant effects on asthma ED visits in the Bronx: maximum 8 hour ozone, 24 hour nitrogen dioxide, 24 hour sulfur dioxide, 24 hour $PM_{2.5}$ and maximum 1 hour $PM_{2.5}$. The results suggest that these pollutants had a statistically detectable impact on acute asthma ED visits in a community with a relatively high baseline rate of acute asthma exacerbations. Significant associations between asthma ED visits and individual $PM_{2.5}$ components were not observed. No statistically significant pollution effects were observed in the Manhattan community. Our findings of more significant air pollution effects in the Bronx likely relate, in part, to greater statistical power for identifying effects in the Bronx where baseline ED visits were greater, but may also reflect greater sensitivity to air pollution effects in the Bronx. In two-pollutant and three-pollutant regression models, ozone and sulfur dioxide, and to a lesser extent, maximum one-hour $PM_{2.5}$, were the most robust pollutants. The more robust health impacts observed for daily maximum $PM_{2.5}$ concentration compared to the 24 hour mean suggest that peak exposures may have larger health impacts. These associations with health effects in the Bronx occurred at ambient air levels that are below the current short-term National Ambient Air Quality Standards.

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Air Pollution Effects on Ventricular Repolarization

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Introduction Previously published work by co-investigator CA Pope, presented evidence that particulate pollution induces changes in heart rate variability (HRV) in elderly patients compromised by pre-existing cardiovascular disease. Ventricular repolarization (the T wave of the ECG) is an established and significant factor in arrhythmogenesis and, moreover, is highly sensitive to heart rate, autonomic tone, chemical/ionic imbalances, and presence of or changes in disease state, e.g., ischemia, heart failure, Long QT Syndrome. Recent work of the P.I. has led to the development of indices of repolarization heterogeneity and rate dependency that can been used to assess dynamic changes in the arrhythmogenic substrate, particularly in patients compromised by disease and those undergoing pharmacological therapy. We hypothesized that the insult of exposure to particulate pollution in patients already at risk would be detected by examining changes in repolarization rate dependency and heterogeneity.

Objectives The overall goal of this project is to measure and assess ventricular repolarization changes in previously recorded, continuous, 24-hour ECG recordings obtained from human subjects during periods of low and high concentrations of ambient airborne particulate matter. The specific aims of the study are 1) to measure, on a beat-to-beat basis, cycle length (RR), RMS (root-mean-square) R peak to T peak interval (RT, an estimate of mean ventricular action potential duration), RMS T width, (TW, an estimate of ventricular repolarization dispersion), QT and QTc, and 2) statistically compare 24 hour time series of CL, RT, TW and QTc and assess differences in RT:RR and QT:RR regression, dynamically over 24 hours. The underlying hypothesis of the proposal is that air pollution (high levels of ambient particulate matter) deleteriously alters ventricular repolarization, independent of heart rate.

Methods 215 previously recorded 2 channel Holter (ECG) recordings were available for this study. Multiple 24-hour recordings were made on elderly patients with pre-existing cardiovascular conditions during "clear" days and days in which there were high concentrations of ambient airborne particulate matter. These digital recordings were processed using a custom program that detected each beat, removed the ECG baseline and calculated the RMS of the signals from which previous cycle length (RR), RT, QT and TW were measured for each beat. Epoch averages of RR, RT, QT, and TW were determined, along with RT/RR and QT/RR regression slopes, offsets, standard errors and correlations which assessed dynamics of rate dependency of repolarization as a function of time. In addition, width of Poincare map (RR_{i+1} vs RR_i) point spread was used to characterize cycle length variation. Finally, epoch index averages were compared statistically using Z scores and F tests for pairs of time-of-day aligned records for each patient.

Data, Findings and Preliminary Results For this new application, we have completed the preliminary data processing and now are comparing recordings during clear and pollution days. We shall also re-analyze the cycle length data to statistically assess changes in heart rate variability which will be compared to the originally published data.

Accountability Analysis of Title IV of the 1990 Clean Air Act Amendments

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Between 1999 and 2002, average ambient concentrations of $PM_{2.5}$ in the United States declined by 10 percent. Over the same period, emissions of SO_2 also declined by two million tons. Both events followed the implementation, beginning in 1999, of Phase 2 of Title IV of the Clean Air Act Amendments (CAAA) of 1990. Our goal is to account for these three occurrences. To connect the policy and the emission changes, we will conduct a careful source-by-source analysis to establish where (i.e., which sources) and when emission reductions occurred, using the U.S. Environmental Protection Agency's (EPA) annual emission inventories and the detailed database of emission transactions maintained by EPA's Clean Air Markets Division. We will use two methods to develop source-receptor matrices to establish a causal relationship between the emission reductions and the improvement in air quality: (i) a statistical model linking sources and receptors, and (ii) a weather-mediated source-receptor matrix based on a large-scale regional atmospheric model. We will then use the models to develop one or more "no policy" counterfactuals against which the observed reductions in ambient $PM_{2.5}$ and SO_4 concentrations can be compared.

Peripheral Microvascular Dysfunction Follows Ultrafine Titanium Dioxide Inhalation

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We have previously shown that pulmonary exposure to fine particulate matter (PM) impairs endothelium dependent dilation in systemic arterioles. Ultrafine PM has been suggested to be more toxic by virtue of its increased surface area. The purpose of this study was to determine if ultrafine PM inhalation produces greater microvascular dysfunction than fine PM. Our inhalation chamber creates stable TiO_2 aerosols at concentrations up to 20 mg/m^3. TiO_2 is a well characterized particle devoid of soluble metals. Rats were exposed to fine TiO_2 via intratracheal instillation or ultrafine TiO_2 via inhalation (mean particle diameters of ~1 µm, and ~160 nm, respectively) at concentrations to produce equivalent pulmonary loads of 0.25, and 0.1 mg/rat. The spinotrapezius muscle was prepared for in vivo microscopy 24 hours after pulmonary exposure. Intraluminal infusion of the Ca^{2+} ionophore A23187 was used to evaluate endothelium dependent arteriolar dilation (micropipette ejection pressures of 5, 10, 20 and 40 psi). In control rats, A23187 infusion produced dose dependent arteriolar dilations that were near maximal at 40 psi. In rats exposed to fine TiO_2, A23187 infusion failed to elicit a significant arteriolar response. In rats exposed to ultrafine TiO_2, A23187 infusion produced dose dependent arteriolar constrictions that were significantly different from the responses observed in rats exposed to fine TiO_2. Bronchoalveolar lavage was performed in a separate group of rats exposed to identical TiO_2 loads. No significant BAL differences were found between PM type or load. These observations suggest that at equivalent pulmonary loads, as compared to fine TiO_2, ultrafine TiO_2 inhalation produces greater remote microvascular dysfunction. This effect may be due to alterations in endothelial integrity and/or signaling.

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

Dosimetry Predictions in a Murine Animal Model of Human Disease

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Particulate matter dosimetry provides the critical link between exposures and the initial doses reaching various sites in the respiratory tract. Because of the difficulty and sometimes ethical concerns of performing mechanism based human inhalation studies on susceptible human subpopulations (children, asthmatics, persons with heart or lung disease, etc.), various animal models are being used to investigate the mechanisms by which ambient airborne particulate matter may effect susceptible sub-populations. The leading mathematical dosimetry programs typically divide the respiratory tract into three regions: extrathoracic airways (nares to larynx); tracheobronchial airways (TB); and pulmonary airways (P). Deposition in the extrathoracic airways is usually derived from empirical fits of in-vivo deposition data as a function of an impaction or diffusion parameters. Deposition in the TB and P airways is typically calculated using sophisticated particle physics resulting in mechanistic deposition equations that define the required anatomical and physiological measurements. The TB and P anatomical data required in the deposition equations include airway length, diameter, branch angle and inclination to gravity. The goal of this study was to provide the necessary anatomical information so predictions of particle deposition could be performed for a widely used model of asthma; the sensitized Balb/c mouse.

Tracheobronchial airway morphometry of sensitized male Balb/c mice was generated from three (from a total of twelve) in-situ prepared lung casts. The airway dimensional artifacts on such casts have been evaluated and shown to be negligible by comparing measurements from in-situ casts with those using tantalum bronchograms in living animals. The distribution of number of generations to terminal bronchiole for each lobe of the lung was determined by assigning a unique binary number to each airway. This enabled the median path length to terminal bronchiole (non-alveolarized airway) to be determined for the typical path airway anatomy model. A total of 25 median length paths to terminal bronchiole were measured (airway length, diameter and branch angle) in each lung cast. These 25 paths were proportionately distributed among the six lobes based upon the number of median length pathways in each cast. Airway length, diameter and branch angle were measured for each airway in the 25 median length pathways. Measurements of airway length, diameter and branch angle for each generation were averaged to create a typical path TB anatomy model. A model of the pulmonary airways was also developed so that particle deposition predictions could be performed for particle diameters of 0.1 – 100 micrometers at several levels of ventilation. Predictions particle deposition efficiency was consistent with deposition measured in-vivo.

*** The Effects of Fine Particle Components on Daily Mortality in Six California Counties: Results from CALFINE**

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Objectives: Several epidemiological studies provide evidence of an association between daily mortality and particulate matter with aerodynamic diameter less than 2.5 microns (PM2.5 or fine particles). Few investigators, however, have examined t the relative toxicity of specific particle constituents. These studies suggest that particles related to combustion may be of primary importance. In this study we examined associations between daily mortality and 22 different components of PM2.5 in six heavily populated California counties.

Methods: We collected daily data from 2000 to 2003 on mortality, meteorology and PM2.5, as well as elemental and organic carbon (EC and OC), nitrates, sulfates, zinc, copper, silicon and manganese. We examined associations of PM2.5 mass and its constituents with daily counts of mortality from all causes and from several disease-specific subcategories, including respiratory, cardiovascular, ischemic heart disease and diabetes. Poisson multiple regression models incorporating natural splines were used to control for time-varying covariates, such as seasonality and weather, that could affect daily counts of mortality. Each component of PM2.5 was individually entered into the model to test for its association with mortality. We combined county-specific effect estimates for each species in a meta-analysis using a random effects model. We also conducted several sensitivity analyses, including (i) stratification by season, (ii) varying the degrees of freedom in the spline smooth of time, (iii) different treatments of missing values, and (iv) alternative specifications of weather.

Results: Among the major findings, concentrations of PM2.5 mass, OC, EC, nitrates, zinc, iron, titanium and potassium were associated with daily mortality from cardiovascular disease. For example, the relative risk of cardiovascular mortality increased by 1% for a single-day change of 10 $\mu g/m^3$ PM2.5 and by about 2% for similar changes in EC, OC and nitrates. In the analysis of colder months, associations with mortality were observed for many of the pollutants, including sulfates and coarse particles. The general results were robust to alternative specifications of time and weather, and to the treatment of missing values.

Conclusions: This multi-county analysis adds to the growing body of evidence linking fine particles with mortality. The results suggest that in California, different components of PM2.5 are associated with mortality, with varying toxicity. Use of PM2.5 mass as a pollutant metric may underestimate the effect estimates of some particulate species with mortality, especially those related to combustion. Pollution from mobile sources, particularly diesels, and from woodstoves appear to be particularly important

* Study not funded by HEI.

Impact of Improved Air Quality During the 1996 Atlanta Olympic Games on Multiple Cardiorespiratory Outcomes

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Considerable evidence supports an association of ambient air pollution and cardiorespiratory morbidity. There is increasing interest in evaluating whether actions taken to reduce air pollution levels will result in reduced morbidity. This project represents a unique opportunity to capitalize on a local intervention effort to reduce traffic in Atlanta during the 1996 Summer Olympic Games. We will comprehensively assess the impact of reduced traffic and ambient air pollution levels during the 1996 Summer Olympic Games in Atlanta on cardiorespiratory morbidity. This project will expand results from a previous study, in which investigators reported reduced Medicaid asthma visits during the Olympics compared to a baseline period. This project will provide a more comprehensive assessment of the health impacts of the reduced air pollution levels during this time period, examining multiple cardiorespiratory health outcomes. The assessment will include two sources of health outcome data, emergency department visits and arrhythmic events, part of an ongoing investigation of cardiac and respiratory visits in relation to daily measures of air quality in Atlanta. The emergency department database includes information on over eight million visits from 41 hospitals in the twenty-county metropolitan Atlanta area over the period 1993 – 2004, including 25,000 visits from 13 hospitals during the Olympic time period (July 19, 1996 – August 4, 1996). Additionally, we have information on visits for all ages, allowing for examination of pediatric as well as other age groups for a range of respiratory (e.g., asthma, upper respiratory infection, chronic obstructive pulmonary disease, pneumonia) and cardiovascular (e.g., congestive heart failure, ischemic heart disease, myocardial infarction, dysrhythmia, and peripheral and cerebrovascular disease) outcomes. A second part of the ongoing study is examining arrhythmic events (ventricular tachycardia and ventricular fibrillation) in patients with implantable cardioverter defibrillators. These events are less likely than the emergency department visits to be impacted by changes in usage patterns during the Olympics. Using these two databases, we will examine healthcare usage patterns during the Olympic time period to inform analytic modeling choices. Specifically we will assess the usage patterns of residents in the five central counties in the Atlanta area to determine if usage patterns changed during the Olympic time period. Additionally, we will compare usage patterns during the Olympic time period to patterns in other years. We will utilize Poisson time-series models to examine the association of the Olympic time period with daily counts of cardiorespiratory emergency visits and arrhythmic events, controlling for time trends and meteorologic conditions. We will evaluate the use of an offset term to control for possible changes in overall emergency department usage patterns by Atlanta residents during the Olympics. This project allows for analysis of the successful effort in Atlanta to reduce traffic, and consequently traffic-related pollution, during the 1996 Summer Olympic Games. This investigation may provide meaningful insights regarding the potential impact of reducing traffic and altering commuting behaviors and subsequently improving air quality on a more permanent basis.

Improved Air Quality and its Influences on Short-Term Health Effects in Erfurt, Eastern Germany

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Ambient air pollution levels decreased tremendously in Central and Eastern Europe during the 1990s. Ambient air quality improved with respect to the criteria pollutants (PM_{10}, $PM_{2.5}$, SO_2, NO_2, CO, and O_3) in these areas. In order to measure simultaneously the health impact we propose to study the association between these pollutants and different health outcomes from 1991 to 2002 in Erfurt, Eastern Germany. Further, the change in particle number concentrations in six size-fractions from 0.01 to 2.5 µm and its effect on mortality will be characterized.

The study has the following specific aims:

1. To relate ambient levels of the gaseous criteria pollutants to the daily mortality for the time period between October 1991 and March 2002 as well as PM_{10}, $PM_{2.5}$ and the size distribution of particles to the daily mortality for the time period between October 1991 and March 1992 and between September 1995 and March 2002,
2. To test whether the relative risks for daily mortality associated with these pollutants remained unchanged over the respective time periods,
3. To test whether changes in concentrations of the gaseous criteria pollutants affected the relative risks for PM_{10}, $PM_{2.5,}$ and ultrafine particle (UFP) number concentration.

Daily mortality and air pollution data were collected and cleaned for the entire study period. Poisson regression models adjusting for trend, season, influenza epidemics, calendar effects, and weather using penalized splines in R were developed. Model fit was based on Akaike's Information Criterion, the absence of autocorrelation in the residuals, and plausibility of the dose-response relationships.

The total study period was divided into three subperiods: period 1 from 10/01/1991-08/31/1995, period 2 from 09/01/1995-02/28/1998, and period 3 from 03/01/1998-03/31/2002. Mean SO_2 concentrations between periods 1 and 3 decreased dramatically by a factor of 12.6. Mean CO and PM_{10} concentrations decreased by a factor of 2.7 and 2.1, respectively. NO_2 concentrations decreased moderately by a factor of 1.46. All decreases were statistically significant.

Key regression results include an association of the UFP number concentration on daily mortality at lag 4 days (Relative Risk (RR) per interquartile range: 1.029; 95 % confidence interval (CI): 1.003-1.055), an association of CO at lag 4 days (RR=1.019, 95% CI: 1.002-1.036), and an association of ozone at lag 2 days (RR=1.046, 95% CI: 1.011-1.083).

Time-varying regression coefficient models support these findings. In addition they indicate that the magnitude of the risk estimate might have changed over time. For example, the RR per IQR increase in CO ranged between 0.98 (95% CI: 0.89-1.07; in 2001) and 1.06 (95% CI: 1.01-1.10; in 1997). For UFP number concentrations, a time-varying association with daily mortality was found whose magnitude shows a seasonal pattern with a RR per IQR ranging between 0.89 (95% CI: 0.68-1.17) in summer and 1.09 (95% CI: 1.01-1.18) in spring.

In conclusion this analysis suggests associations of UFP with daily mortality which might have changed over time with changing air pollution patterns. Further analyses to relate these changes to changes in the emission sources are ongoing.

*** Childhood Asthma and Respiratory Health in Latino Children in the El Paso Airshed**

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The National Institute of Environmental Health Sciences (NIEHS) has initiated support for a multi-disciplinary, multi-institutional investigation of asthma in Latino children, ages 5-17, in the El Paso, Texas community. The project focuses on the relationship between air and environmental quality at the neighborhood level and the incidence and prevalence of asthma among the largely Mexican-American population of the region. This ARCH (Advanced Research Cooperation for Environmental Health) Program links researchers at the University of Texas at El Paso with their counterparts and specialized research facilities at the University of New Mexico Health Science Center.

The core 5-year project examines the hypothesis that air and soil pollution is associated with asthma and respiratory health in medically underserved Hispanic-Latino children in the El Paso border region. Activities include air monitoring, household surveys, collection of health data, and development of a cohort of asthmatics and controls.

High-density outdoor particulate sampling, using dichotomous monitors will provide seasonal and geographic data to interface with asthma exacerbation records. Levels of nitrogen dioxide, ozone, and volatile organic compounds also will be measured at these outdoor sites. Continuous monitoring, over 1-to-2 week periods, of particulate matter in indoor and outdoor air at specific homes throughout El Paso will provide baseline data on potential exposure to asthma-causing material.

One supporting project uses impulse oscillometry to evaluate the effect of air quality on respiratory function in normal and asthmatic Anglo and Hispanic children. Impulse oscillometry (IOS) is a promising new, non-invasive technique for measuring lung function, well suited by its clinical simplicity for evaluation of children.

Researchers also will evaluate the role of environmental PAHs in air and soil as potential triggers of asthma using biological assays associated with known or suspected pathways of asthma exacerbation. Local variation in bioactivity of the material will be compared to regional asthma patterns. An investigation of ultrafine PM will quantify the concentrations of carbon nanotubes that home combustion sources—cooking, and water and space heating—contribute to indoor and outdoor air. The toxicological effects of purpose-generated carbon nanotube aggregates on human alveolar macrophage and bronchial epithelial cell lines will be evaluated.

* Study not funded by HEI.

Modification of Extreme Hot Weather on Effects of Ambient Particle Pollution on Cause-Specific Mortality in Wuhan, China

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Our previous studies in Wuhan, China have demonstrated significant effects of long-term ambient air pollution on respiratory health among children and adults. However, no study has been carried out in Wuhan to determine the acute effects of ambient particulate matter (PM) air pollution on mortality. This study, funded by the Health Effects Institute as part of the Public Health and Air Pollution in Asia Project (PAPA) is intended to determine the acute effects of ambient PM pollution on mortality, and to investigate the effect modification of the extreme hot weather on the pollution mortality effects in Wuhan, China.

Wuhan is a large city with 4.3 million permanent residents living in its nine urban core districts. Historically, Wuhan has been called "a stove city" in China because of its hot summer. We retrieved city-wide daily air pollution data, meteorological data, and mortality data for the four years from July 1, 2000 to June 30, 2004. Under the assumption that daily death counts follow a Poisson variate with constant over- or underdispersion, we used quasi-likelihood estimation within the context of the Generalized Additive Models (natural spline models in R) to model the natural logarithm of the expected daily death counts as a function of the predictor variables. We performed time-series analysis to associate daily nonaccidental mortality with daily mean PM_{10} concentrations, controlling for important covariates including gaseous pollutants SO_2, NO_2, or O_3. We also examined the interaction between extreme hot weather and PM_{10}.

For a 10 $\mu g/m^3$ increase in PM_{10} at lag 0 days, we observed an elevated risk of total nonaccidental cause mortality (0.28%; 95% CI 0.09% - 0.46%), total nonaccidental mortality with age over 65 (0.32%; 95% CI 0.11% - 0.54%), cardiovascular mortality (0.42%; 95% CI 0.17% - 0.66%), and respiratory mortality (0.73%; 95% CI 0.15% - 1.32%). We also observed significant interactions between PM_{10} and extreme hot weather, in the direction that the presence of extreme hot weather enhanced the effects of PM_{10}

These results confirmed that ambient PM pollution has a significant effect on mortality in Wuhan China, which is consistent with the finding from other studies. Furthermore, our findings suggest that the PM_{10} mortality effects were enhanced by the presence of extreme hot weather. Future studies will be conducted to determine whether the results reported above would be modified by other important factors, such as socioeconomic position.

Multi-City Study of Air Pollution and Health Effects in Latin America

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The overall goal of this project is to use a common analytic framework to examine the association between exposure to outdoor air pollution and health effects in several Latin American and Caribbean (LAC) cities, in order to obtain comparable and updated information on effects of air pollution on several age/cause groups. This will be achieved through developing a common protocol for the design and analysis of time series data to be followed by all centers involved in the project. An important focus will be the detailed examination of the impact of such exposures in specific subgroups of the population considered most vulnerable such as infants and young children and the analysis by socioeconomic position.

In the first steps we will collect data and perform quality assurance for air pollution and mortality data from the participating cities from Brazil, Mexico and Chile. Candidate cities so far are: Mexico City, Guadalajara, Toluca, Monterey and Juarez City (Mexico); Sao Paulo, Rio de Janeiro, Porto Alegre and Vitoria (Brazil); Santiago, Antofogasta, Calama, Copiapo and Temuco (Chile). Assessment of the availability and completeness of data in other large Latin American cities will also be pursued and those who fit the inclusion criteria will be included.

Descriptive data of air pollutants and frequency distribution of mortality by cause and age groups will be carried out. First single-city analysis will be conducted using a standardized analytical protocol (first stage analysis). Heterogeneity will be explored and data combined using meta-regression models (second stage analysis). Overall and subgroup analyses will be conducted using Generalized Additive Models (GAM) in Poisson regression.

We will also explore the potential effect modification of socio-economic position (SEP) and other variables on the association of air pollution and mortality using multi-level modeling (second stage analysis). A common SEP indicator will be identified that can equally represent the SEP of populations in the different cities.

This project aims to contribute to the international scientific discussion on the conduct and interpretation of time-series studies of the effects of short-term exposure, and to provide relevant information to decision makers in the LAC Region to support prevention and control strategies of air pollution

Air Pollution and Health: A Combined European and North American Approach (APHENA)

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The project brings together the investigators who have carried out the Air Pollution and Health: A European Approach (APHEA 1 and 2) studies, the National Morbidity and Mortality Study (NMMAPS) in the United States, and national studies in Canada. The findings of these studies have substantial implications for public health policies directed at controlling health effects of air pollution; each has shown adverse effects of air pollution on morbidity and mortality at current concentrations of air pollution in Europe and North America. A principal objective of APHENA is to characterize heterogeneity in the effects of particulate matter on mortality and morbidity across the included cities. The principal goals include 1) development of core models for the first-stage (within-city) analyses of time-series data on mortality and hospitalization for the APHENA cities; 2) development of harmonized data bases on potential modifying factors across the cities; and 3) parallel and combined analyses of data on air pollution and mortality and morbidity, with exploration of heterogeneity in the effect of particulate matter and its determinants.

There have now been multiple meetings and exchanges to develop a protocol for first-stage (within-city) analyses, to review findings of these analyses, and to carry out second-stage analyses. The approach to the first-stage analyses is based on initial simulation studies and extensive exploratory and sensitivity analyses. The decisions taken specified the outcome categories, pollutants, core models, and sensitivity analyses. Additionally, a set of potential effect modifiers for the second-stage analysis was identified. The first-stage analyses have been completed for mortality and hospitalization and second-stage analyses are being completed for mortality. The results provide estimates for exposure to PM_{10} and ozone and outcomes including the daily total, CVD and respiratory numbers of deaths by age categories. Several models have been applied with varying degrees of freedom and smoothers and results compared. For PM_{10}, estimates are generally similar in the United States and Europe; for ozone, estimates tend to be higher in the U.S. compared with Europe and the highest in Canada. The second-stage analyses tests whether factors representing pollution and population characteristics explain heterogeneity of first-stage estimates. Updated findings will be presented at the HEI Annual Meeting.

A Web-based Database of Fine Particulate Matter and Related Data for Health Effects Studies

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EPA promulgated National Ambient Air Quality Standards (NAAQS) for fine particulate matter (PM) with aerodynamic diameter less than 2.5 micrometers ($PM_{2.5}$) in 1997. Routine monitoring of $PM_{2.5}$ and speciated $PM_{2.5}$ started in 1999 and 2000 in order to establish compliance status and to support the formulation of control strategies for areas out of attainment. Since then, a rich data set has become available that can be used to support health effects studies. The objective of this project is to create a user-friendly database for health effects researchers to access and analyze these $PM_{2.5}$ and speciation data in conjunction with other related data, including gaseous pollutants and meteorological parameters, that are useful for deciphering the relationships between $PM_{2.5}$ (and its components) and health endpoints.

In Phase 1 of the project, speciation trends network (STN) sites were characterized based on their location, monitoring objective, surroundings, and data characteristics. Possible measurement uncertainties were identified and compiled in a report. Based on $PM_{2.5}$ composition data, several urban areas with different $PM_{2.5}$ characteristics were identified and recommended for the study of health effects related to several $PM_{2.5}$ components. Spatial variability was characterized using $PM_{2.5}$ mass concentration data as well as speciation data.

In Phase 2, a database was designed and created in MySQL together with a web-based interface to serve as the front end of the database. The website contains a map of the available STN and supplemental sites for PM data. Time series of $PM_{2.5}$ concentrations can be obtained by clicking on an individual site. The user selects a list of sites based on site characteristics data that have been compiled in Phase 1 (e.g., site location, monitoring objectives, population and level of local emissions) or based on measurements that satisfy specific criteria (e.g., statistical properties of the concentration data, data completeness, availability of co-located gaseous and meteorological data). From the database, the user can query the database for $PM_{2.5}$ mass and speciation, ozone, carbon monoxide, sulfur dioxide, nitrogen oxides and meteorological parameters, and download data files containing the selected parameters. The database/website system was launched in September 2005. Since the launch, the website has been cited by *Science* magazine (13 January 2006, p.153) and accessed by over a hundred users from government agencies, universities, non-profit organizations, and industry.

Source Apportionment and Speciation of Particulate Matter for Exposure and Health Studies

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Assessment of actual human exposures to organic compounds and trace metals in atmospheric particulate matter is very important to understanding potential health impacts. While techniques for analysis and speciation of ambient particulate matter samples have progressed, the low mass loadings of samples from personal exposure monitors still present challenges. The objectives of this project are to optimize organic and trace metals speciation methods for the low mass particulate matter samples collected by personal samplers, and to integrate the validated methods for sample collection and analysis with epidemiology studies.

As part of this project, two methods have been developed to allow the analysis of organic compounds in personal exposure samples. A Thermal Desorption GCMS (TD-GCMS) analysis for non-polar compounds including polycylic aromatic hydrocarbons (PAH), hopanes, steranes and n-alkanes was adapted for the analysis of personal exposure samples. In addition, a second method was optimized for personal exposure samples that allowed the analysis of polar and non-polar organics compounds, which integrated traditional solvent extraction sample preparation with high-volume GCMS sample injection to improve detection limits.

For trace metals analysis, the existing UW-Madison ICPMS analysis for personal exposure samples has focused on an improved low volume acid digestion that allows further reduction of contamination and the expansion of the digestion to include silicon. Method improvements included validation of a low volume acid digestion that required a modified microwave digestion program, a decrease in digestate dilution volumes, and the validation of a new digestion vial. In addition, methods have been developed for the speciation of iron, chromium and manganese using both wet chemistry and synchrotron techniques, which can be used with personal exposure samples.

The current focus of the project is the integration of the methods that were developed as part of the study with ongoing exposure and health effects studies. The methods developed for personal exposure sample analysis will be presented in the context of how they can be integrated into exposure and health effect studies.

Air Toxics Hot Spots and Traffic Exposures

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The major focus of the study team was to finish processing the samples collected during 12 week long site visits, and to build the Oracle database and statistical framework for the data analysis using particle data that would later extend to aldehyde and VOCs. During a halt in field testing, a major effort was devoted to refining the statistical methods for analyzing this complex data set.

Methods: An approach using structural equation models (SEM) was used to explore our large set of particle data, which was collected with the sample sampling strategy. A principal component analysis (PCA) using the collected VOCs, aldehydes, and particle data was used to determine several independent factors within the many correlated descriptive variables for the sampling sites. We have also begun to examine the Tobit model as a method of handling variables where there is a significant fraction of the data that is less than detectable.

Results: A three tiered SEM was substantially better at predicting personal job exposures (R^2=0.6) than a step-up or step-down regression because it better accounted for the complex covariance structure of the data. The PCA analysis of concurrent data on 17 VOCs identified four factors (combinations of variables) that accounted for 69-76% of the total variability in the concentrations. The grouping patterns for the yard samples were very similar to those for the non-smoking drivers; smoking drivers were somewhat different. The first factor VOCs (trimethyl- and methyl-pentanes, benzene, ethyl benzene, and xylene) were most strongly correlated with all of the particle exposures ($PM_{2.5}$, elemental carbon and organic compounds). All of these analyses show the strong influence of vehicle emission sources, cars and diesel trucks. Because of the short time scale of wind direction variability, up and downwind sampling with integrated 12 hr collections gave poor resolution of upwind sources, although the effects of some major local sources were detected.

Spatial Distribution of Air Toxics near a U.S. Border Crossing

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An exposure assessment of ambient air toxics from vehicular emissions was conducted in West Buffalo, a neighborhood adjacent to the Peace Bridge, a major US-Canada border crossing. The findings and methods implemented in this study should be relevant to other similar mobile-source hot spots, such as those along the U.S. borders with Mexico, and other locations of intense vehicle traffic, such as ports. Understanding the spatial distribution of the concentration profile for pollutant levels in and around a highly trafficked area should provide insights into estimating exposures on an individual household scale around "hot spots". Our objective is to develop neighborhood scale maps showing statistically estimated pollutant concentration profiles, and to characterize the extent and severity of air toxics exposure in Buffalo neighborhoods adjacent to the Peace Bridge Plaza. We chose ultrafine particle count measurements and total particle bound polycyclic aromatic hydrocarbons (pPAHs) for our maps. These contaminants serve well as traffic indicators, represent exposures of interest, and provide the ability to detail spatial and temporal patterns within local neighborhoods.

Measurements were taken during July 18-31, 2005 and January 9-21, 2006. Sampling measurements included speciated 12-hour integrated (VOCs, elements, PAHs) and continuous real-time monitors at three fixed sites. Small scale variations in concentrations across space were measured using four sets of mobile, portable continuous monitors containing a TSI P-Trak (ultrafine particle counter), an ECOCHEM PAS 2000CE (photoaerosol sensor for pPAHs), a GPS (to record measurement location), and a PEM for mass and elemental analyses. Estimated surface concentration profiles for particle counts and pPAHs were produced using a generalized additive model (GAM) in R (R: A Language and Environment for Statistical Computing). ARCGIS™ (ESRI, Inc.) was used to produce surface maps.

Contributions of air toxics from vehicle emissions at the Peace Bridge/I-190 complex from volatile organic compounds (VOCs) and polycyclic aromatic hydrocarbons (PAHs) over the entire sampling period were well in excess of locally measured background levels. The relative proportions of these levels vary over time and meteorology, and across species. Similarly integrated measurements of VOCs, and PAHs followed a similar pattern. The pPAH levels decreased rapidly by street, as distance increased along the average downwind vector. Levels within 1 km of the source ranged from 6 – 30 ng/m^3 dropping off rapidly after 250m. Particle counts also varied greatly over space but a distinct signature over time was not apparent.

The difference in the measured average behavior of particle counts and pPAHs is likely due to the fact that ultrafine particles are a near-field phenomena and the PAS2000CE measures pPAHs in the 1 – 2 um size fraction which is stable over greater distances thus reducing the impact of local traffic to the measurement. Over shorter times and conditioned on meteorological parameters, both instruments are good surrogates of spatial variations of traffic emissions. As PAH average concentrations drop off rapidly from a large source, we would conclude that many fixed-site urban monitoring systems will not characterize mobile-sources related air toxic exposures that have substantial heterogeneity.

*** A Study to Evaluate Improvements in Health Outcomes from Incremental Improvements in Air Quality in Southern California**

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Considerable effort has been expended to reduce ambient air pollution, with the expectation that such reductions would have a beneficial effect on human health over the long-term. This hypothesis has never been tested directly. The health benefits study's primary aim is to test it with data on cardiac, cardiovascular and respiratory mortality and morbidity as measured by hospital discharges and mortality in the Los Angeles basin between 1980 and 2000. Marginal Structural Models (MSMs) have typically been used to investigate the effects of treatments/exposures on selected outcomes but are also natural tools in this context. By definition, MSMs model the population outcomes under counterfactual exposure scenarios. In particular, we can infer from such models about population health outcomes had the effort to reduce air pollution in the Los Angeles basin been something other than it was—i.e., air pollution had not decreased as much as was observed in the data. In addition and unlike conventional association models, MSMs enable proper adjustment for time-dependent confounders (including co-pollutants, demographic factors) that also are on causal pathways between the pollutants of interest and health outcome. Specifically, the data assembled in this study integrate exposure, demographic and public health variables for 195 geographical units from the Los Angeles basin monitored quarterly over 20 years. Characterization of lag effects of pollutants thus presents particular analytical challenges when applying MSMs and a new class of marginal structural models (history-restricted MSMs) has been developed to allow for a more flexible investigation of lag effects. These models minimize implementation issues as well as statistical power concerns in longitudinal studies. In this presentation we will: 1) illustrate the statistical approach in this study with preliminary analyses; 2) motivate and introduce History-restricted MSMs, 4) discuss the assumptions on which proper MSM estimation relies specifically in the context of studies of long-term health benefits related to declines in ambient air pollution. Although not discussed in this abstract on important goal of the study is use the health outcome analysis to estimate the economic value of any health benefits found to be associated with improved air quality.

* Study not funded by HEI.

*** Highway Traffic Near Residence Associated with Altered Pulmonary Function Among Children with Asthma: Results from the Fresno Asthmatic Children's Environment Study**

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Background: Exposures to traffic-related pollutants, such as nitrogen dioxide, or daily traffic counts have been associated with transient changes in pulmonary function in the short-term, and implicated in reduced lung function growth over the long-term. As part of a study to characterize the effects of air pollution exposures on a cohort of children with asthma in Fresno, California, a cross-sectional analysis was conducted to evaluate the association between pulmonary function and highway traffic near residences. The ratio of forced expiratory flow between 25 and 75% of vital capacity to forced vital capacity (FEF_{25-75}/FVC), which reflects small airway resistance, was used to evaluate the modifying effects of small airway function.

Methods: Data were available for 214 children (ages 6-to-11 years old at enrollment). Baseline spirometry data were obtained with a dry rolling-seal spirometer. Sex and race/ethnicity-specific percent-of-predicted values were computed with reference equations from the third National Health and Nutrition Examination Survey. Traffic data were obtained from the California Department of Transportation. Multiple linear regression was used to evaluate the relations between pulmonary function and distance-of-residence to the nearest highway, annual average daily traffic count (AADT) on that road, or the inverse-distance-weighted-AADT (IDWT), and a surrogate measure of diesel-related exposures. Among the covariates included in final models were markers of socioeconomic status. Modification of IDWT effects by small airway function was evaluated by inclusion of an interaction term (IDWTxFEF_{25-75}/FVC) in final models.

Results: After adjustment for covariates, pulmonary function was positively associated with longer distance-to-road and negatively associated with traffic measures that capture traffic intensity (count). For example, the ratio of forced expiratory volume in 1 second to FVC (FEV1/FVC%) %predicted increased with greater distance-to-road (0.84%, 95%CI: -0.53%, 2.22%; regression coefficients scaled to distance interquartile range (IQR)=1,439 meters), and decrease with increases in IDWT (-0.57%, 95%CI: -1.13%, -0.02%; coefficients scaled to IDWT IQR=73.7) and AADT (-1.67%, 95% CI: -3.39%, 0.05%; coefficients scaled to AADT IQR=44,911). When we evaluated effect modification by FEF_{25-75}/FVC, all pulmonary function measures of flow were significantly inversely related to IDWT. The interaction term regression coefficients were positive (and significant) indicating a diminished effect of traffic the larger the FEF_{25-75}/FVC ratio.

Discussion and Conclusions: The results indicate that residence proximity to highway traffic may be associated with deficits in pulmonary function among children with asthma. A novel finding is that smaller airway size appears to be an important modifier of the effect of traffic on pulmonary function and a potential marker of greater susceptibility.

* Funded by: The California Air Resources Board and the U.S. Environmental Protection Agency

Time Series Study on Air Pollution and Mortality in Delhi, India

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Introduction: The cities of India form parts of the polluted mega-cities of the world and traditionally are the habitat of millions of urban dwellers. In recent years, several actions have been taken to address the growing air pollution problem in Indian cities, mainly in the capital city of Delhi, which has suffered for decades from declining air quality. However, studies to assess the health impacts of air pollution in Indian cities are sparse. In order to bridge the gap in scientific knowledge and add to the ongoing studies in other Asian cities, a retrospective time series study on air pollution and mortality in Delhi has been initiated under the PAPA program.

Objectives: i) To obtain the time series data on air quality parameters, mainly Respirable Suspend Particulates with 10 micron cut-off (RSP or PM_{10}) and all cause natural deaths and evaluate the relationship between the two in Delhi. ii) To quantify the change in mortality in relation to changes in air quality in a multivariate model after controlling for the confounding factors.

Methodology: The ongoing study uses a retrospective time series data (3 years data) on air quality and registered data on deaths in Delhi to study the changes in daily death rate due to change in air quality levels. The methodology involves collection of: (i) data on ambient air quality for major criteria pollutants for all monitored stations for the period of 2002 – 2004 and evaluate the site selection criteria to determine the suitable sampling location(s) that could represent the population exposure in the city of Delhi. (iii) Collection of meteorological data (temperature, humidity and visibility) for the study period; (iv) collection of daily death records from the Registrar of Births and Deaths and data cleaning. (v) Statistical analysis by adopting common protocol with city specific modifications.

Results: Preliminary results/findings reveals that daily air quality data are available for two stations (out of total eleven) only. Among the three criteria pollutants being regularly monitored, RSP is of concern as the concentration exceeds the National Ambient Air Quality Standard of 100 $\mu g/m^3$ for most of the monitored days. Significant seasonal variation exist specially in case of RSP. The coefficient of correlation for RSP between various monitoring stations lies in the range of 0.4 to 0.7. From the meteorological data it has been observed that the minimum temperature in Delhi goes as low as 3 degree Celsius during winter season and in summer the maximum temperature is recorded as high as 46 degree Celsius. RSP with average visibility showed moderate, negative correlation. Daily total death count varies from 170 to 368 with an average daily death count of 234. Time series analysis to study the inter relationships is under progress.

Estimating the Mortality Effects of Air Pollution in Bangkok, Thailand

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A few studies have examined the relations of air pollution and daily mortality in Southeast Asia where chemical composition, demographics, activity patterns and background health status are different from that in North American and Western Europe. As part of the multi-city PAPA project, we conducted a time-series study to investigate the acute effects of air pollution on daily mortality in Bangkok, Thailand, from 1999 to 2003. We used generalized additive Poisson regression model accounting for temporal trends and meteorological conditions using a natural spline smoother in R software. In the basic model we used 6 degrees of freedom (df) in the smooth of time and 3 df for both temperature and humidity. For a 10 ug/m3 increase in PM10, we observed a 1.2% (95% CI= 0.8%, 1.6%), a 1.7% (95% CI= 0.7%, 2.7%), and a 1.3% (95% CI= 0.1%, 2.6%) increase in mortality from natural causes, cardiovascular diseases, and respiratory diseases respectively. We observed non-significant effects of PM10 on mortality from natural causes among children under 5 years old, whereas a significant and strongest effect was among those aged 65 and over. Gaseous pollutants were non-significantly associated with mortality from the three major causes. The results of sensitivity analysis suggested that the results are insensitive to choices of model specifications. These preliminary results suggest that acute exposure to PM10 increases the risk of mortality in Bangkok. We will next examine impacts of economic recession in Thailand during 1997-1998 on air pollution and mortality.

*** The San Joaquin Valley Aerosol Health Effects Center – An EPA PM-Health Center**
AS Wexler, KE Pinkerton, MV Fanucchi, DW Wilson, and others

University of California, Davis, California

Objectives: The center will investigate the mechanistic links between ambient particles and the health effects that they elicit. This objective entails two goals: (1) Understanding the metabolic response of tissue and organs when they are exposed to particulate pollutants, and (2) understanding the characteristics of the particulate pollutants and their gaseous co-pollutants that elicit these responses.

Experimental approach: The center is composed of five projects supported by five cores. The projects will investigate the metabolic response to pollutant exposure in pulmonary and cardiovascular tissues, whole animal effects of exposure, transport of particles from the airways to other tissues, and the effects of particles and gases on lung development in juveniles. The projects will take both top down approaches, identifying the characteristics of particles that elicit health responses, and bottom up approaches, examining the metabolic responses that these particles elicit. We will perform both field and laboratory studies. The field studies will take place in the San Joaquin Valley of California, one of the worst violators of the National Ambient Air Quality Standards for particulate matter. The laboratory studies will examine the effects of particles from sources or laboratory-generated particles with carefully controlled properties that model ambient ones or those from dominant sources. The research team, composed of physiologists, toxicologists, chemists, and engineers who already collaborate on air pollution studies in the UC Davis Air Quality Research Center, will use their complementary skills to address the center's objectives.

Expected results: Epidemiological studies show a correlation between elevated particulate matter concentrations and increased rates of morbidity and mortality, but these studies do not suggest the mechanisms or the particle properties that cause this correlation. The center's scientists will investigate the properties of the particles that are responsible for these health effects, the metabolism that underlies these effects, and the consequences of chronic exposures, especially during childhood, that make individuals more susceptible to adverse effects.

* Study not funded by HEI.

Interaction Between Air Pollution and Respiratory Viruses: Time-Series Studies for Daily Mortality and Hospital Admissions

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Background: In the Public Health and Air Pollution in Asia (PAPA) project, Hong Kong is one of four cities commissioned to conduct a 2-year study on short-term effects of air pollution on mortality and hospitalization for the period 1996-2002. It will also examine the confounding and interacting effects of influenza and socio-economic groups on the effects of air pollution.

Objectives: (i) To assess the main effects of air pollution on mortality and hospitalization. (ii) To assess the main effects of influenza on mortality and hospitalization. (iii) To assess the possible confounding of influenza on estimated air pollution health effects. (iv) To assess interaction between effects of air pollution and influenza.

Data and methods: Daily counts of mortality and hospitalizations were retrieved from routine data of the Census and Statistics Department and Hospital Authority of Hong Kong. Daily averages of air pollutant concentrations and meteorological conditions were derived from the Environmental Protection Department and Hong Kong Observatory. Weekly numbers of specimens positive for influenza viruses A and B (Flu A+B) and respiratory syncytial virus (RSV) were obtained from the Microbiology Laboratory of Queen Mary Hospital, Hong Kong. Three measures of influenza were derived as Flu A+B and RSV data. Poisson regression core models for daily health outcomes were fitted, using natural spline to adjust for seasonality and covariates temperature and relative humidity. Adequacy of models was assessed by partial autocorrelation function plots. 15 pre-defined models for mortality and 60 models for hospitalization outcomes, all at 5% significance level two-tailed, were used to assess main effects of air pollution and influenza, and confounding and modifying effects of influenza on air pollution effects.

Results: (i) Significant excess risks (ER) of mortality of around 0.5 to 1.5% per 10 $\mu g/m^3$ increase of pollutant concentrations were found in non-accidental causes, cardiovascular disease as well as respiratory disease. Significant ER of hospitalization were also found with magnitude similar to those of ER of mortality. (ii) Influenza was shown to confound the ER of mortality associated with air pollution, especially by SO_2. (iii) In terms of mortality, influenza interacted with SO_2 positively for respiratory diseases and lower respiratory infections, but negatively for heart disease. In terms of hospitalization, influenza tended to interact positively with gaseous pollutants (O_3, SO_2 and NO_2), and negatively with particulates (PM_{10}).

Interpretation and conclusions: Air pollution has effects on mortality and hospitalization with magnitudes analogous to those from other studies. Influenza may be a potential confounder as well as an effect modifier in the assessment of air pollution effects.

Public Health and Air Pollution in Asia (PAPA) – A Multi-city Study for Short-term Effects of Air Pollution on Mortality

HD Kan (Shanghai), ZM Qian (Wuhan), N Vichit-Vadakan (Bangkok), and CM Wong (Hong Kong) *(This study established the protocols and methods for gathering and analyzing data that were followed in each of these four cities. See also the individual abstracts for these Principal Investigators.)*

Background: In a collaborative study for Public Health and Air Pollution in Asia (PAPA), a common protocol was developed among 4 cities in Asia. Individual teams followed the guidelines for development of core models and assessment of the effects, taking into account city specific conditions.

Objectives: (i) Establish a common protocol and apply estimation methods for short-term effects of air pollution in Asian cities. (ii) Assess the effects of air pollutants on mortality within each city and the pooled effects in all the participating cities.

Data and methods: Daily counts of mortality for non-accidental causes (all ages, 0-4, 5-44, 45-64 and 65+ age groups) and cardio-respiratory diseases (all ages) were modeled by *Poisson regression*. Trend and seasonality using smoothers of *natural spline* with 4-6 degrees of freedom, temperature and relative humidity using smoothing spline each with 3 or 4 degrees of freedom, and days of the week and other city-specific conditions using dummy variables, were adjusted for in a *core model* for each health outcome. Adequacy of the core models was evaluated by partial autocorrelation of the residuals. The effects of daily air pollutant concentrations of PM_{10}, NO_2, SO_2 (24 hour average) and O_3 (8 hour average) were estimated.

Results: Preliminary findings were that ambient concentrations for PM_{10} varied across the 4 cities with mean levels of 52.1 $\mu g/m^3$ (Bangkok), 51.6 $\mu g/m^3$ (Hong Kong), 102.0 $\mu g/m^3$ (Shanghai), and 141.8 $\mu g/m^3$ (Wuhan).Significant excess risks were observed across the 4 cities, ranging from 0.2 to 1.1% per 10 $\mu g/m^3$ increase of PM_{10} for non-accidental causes in all ages, with highest excess risk found in Bangkok followed by Hong Kong, Wuhan and Shanghai.

Interpretation and conclusions: Asian cities, like many other cities in other parts of the world, suffer similar effects of excess mortality associated with increased air pollution. Despite stringent regulations put in place from local agencies to control air quality, there is clear evidence of the need for legislation to support a comprehensive program of air quality controls to reduce adverse health effects associated with pollution.

Molecular Effects of Diesel Exhaust Particulates on Respiratory Neutral Endopeptidase in Carcinogenesis

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Neutral endopeptidase *(NEP)* is a 90-110 kDa zinc-dependent, type II integral membrane protein abundantly expressed on airway epithelial cells that plays an important role in the maintenance of homeostasis and may have a role in neoplastic transformation and tumor progression. Little information is available about its relevancy after diesel exhaust particulates (DEP) exposure. In this study, we firstly analyzed temporal/concentration patterns of normal, non-cancerous human airway epithelial cell line BEAS-2B after exposure to standard DEP (SRM 2975, at non-cytotoxic concentration). Data show that the *NEP* mRNA levels decreased in a time-dependent manner during 24 h DEP incubation. The significant change was detected as early as 8 h after DEP addition, persisting up to 24 h. To examine the sensitivity and specificity of *NEP* mRNA responses, we conducted a dose-effect experiment at concentrations of 0 (air controls), 5, 10, 20, 40, 60 μg/ml DEP. After 24 h exposure, *NEP* mRNA exhibited a concentration-dependent downregulation, with a maximum effect beginning at the exposure concentration of 40 μg/ml. Moreover, *NEP* protein and activity also decreased in a concentration-dependent manner after 24-h incubation. To determine whether the repression of *NEP* by DEP occurs at the transcriptional or post-transcriptional level, we assessed the effect of DEP on *NEP mRNA* transcript stability. BEAS-2B cells were treated with actinomycin D, exposed to DEP (40 μg/ml) or vehicle, and then assayed for *NEP* mRNA levels at various time points up to 24 h. Real-time PCR indicated no difference in the rate of *NEP* mRNA degradation between DEP and vehicle-treated samples, thus demonstrating that DEP regulation of *NEP* gene expression likely occurs at the transcriptional level. We also examined the effect of *NEP* knock-down on proliferation of BEAS-2B cells by using siRNA transfection technique. *NEP* siRNA transfectant cells grew slower *in vitro* than control siRNA transfectant cells after DEP exposure. Data show that the proliferation of *NEP* siRNA–infected BEAS-2B cells was significantly inhibited at 2 days of transfection with increased DEP concentrations ($P < 0.01$) and the net proliferation inhibition rates at 5, 10, 20, and 40 μg/ml DEP were 1.4%, 7.6%, 10%, and 14.4 %, respectively, when compared with their mock controls. This finding suggests that *NEP per se* is involved in cell proliferation in the presence of DEP stimulation. Collectively, our study indicates that DEP exposure resulted in NEP expression down-regulation through a transcriptional mechanism that was clearly associated with cell proliferation, an important process of carcinogenesis. These experiments may not only reveal a novel mechanism of carcinogenesis of DEP, but also provide information about *NEP* as a possible exposure biomarker to perform risk assessment. Decreased or loss of *NEP* expression/ activity may indicate a greater susceptibility to the risk of cancer (Supported by HEI).

* Identifying the Role of Organic Compounds in Air Pollution/Health Studies

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Organic particulates are a significant component of particulate matter in urban air pollution. Organic compounds can exist in a particulate state, a semi-volatile state, or in a gaseous state in which these compounds can be attached to particles which enter the airways. Measurements to date of these compounds are limited and often rudimentary, frequently measured as elemental carbon (EC) and organic carbon (OC), which is a broad category containing thousands of different compounds. The existing literature reports several associations between these measures and health outcomes; however, these results have not always been consistent. One possible reason is that the available measures are a collection of many different compounds, likely of highly variable toxicity. Hence even though components of OC may be toxic, it is possible that the collective measure of these compounds may not detect health associations because this measure can be influenced by the presence of innocuous components in the collective measure. One objective of this research is to learn whether some components/fractions of organic compounds are of greater concern for public health.

There are several ways to address this issue. Additional measures of organic compounds can be made, and these can be considered in analyses of epidemiological data. Subsets of the collective measures may help identify the categories or classes of compounds associated with health responses. Alternatively artificial environments which simulate real environments can be created. Physiological responses in these environments can identify those conditions (and the compounds associated with them) most highly associated with adverse responses. These can be studied further in targeted assays to identify compounds or classes of compounds that are specifically associated with responses.

Detailed measurements of organic compounds have been undertaken in Atlanta and St. Louis. Principal components analysis of the Atlanta data indicate that at least 5 major components of organics can be identified. Initial analyses of these components demonstrate different associations with measurements of health response suggesting that some organic compounds are of greater concern than others. Toxicological studies of several reconstructed environments demonstrate differences in toxicity; the characteristics of these environments suggest the importance of organic components as well and provide some insight on the nature of those components of greatest concern.

* Study not funded by HEI.

Short-term Exposure to Diesel Exhaust Leads to Asthma Worsening: Evidence from A Real-world Study

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Many people, including asthmatics, experience short-term exposures to diesel exhaust (DE) in their daily activities. Health effects of such exposures, however, remain poorly documented. In this study, we utilize a real-world setting to examine whether a short-term DE exposure will (1) worsen asthma symptoms, (2) augment airway inflammation, and (3) increase oxidative stress burdens. We also attempt to examine dose-response relationships for several key DE components (e.g., ultrafine particles, elemental carbon, NO_2) and the contribution of background asthma severity to the susceptibility on DE effects.

The study utilizes a natural "exposure chamber", Oxford Street in London, UK. In this street canyon, only buses and taxi cabs, all diesel-powered, as well as pedestrians, were allowed to travel during daytime hours. The street had the highest density of traveling and idling buses in London. Only ~1.5 km away from this street is Hyde Park where motor vehicle traveling is prohibited. A section of this park was used as control site for the study. Significant differences in $PM_{2.5}$, ultrafine particles, elemental carbon, and NO_2 were observed between the two sites. The difference in ultrafine particle number concentration, however, was substantially greater than the difference in $PM_{2.5}$ mass concentration. As planned, adult non-smoking subjects, 30 with mild and 30 with moderate asthma, participated in the study. Each of them completed three study visits. In the first visit, the subject completed a set of health screening tests at a local hospital. During the second and third visits, after measurement of baseline health status in the hospital, the subject traveled to either the street or the park (random in order), where they walked for 2 hours at a steady pace within defined boundaries, and then returned to the hospital for 6 and 24 hour post exposure measurements. Health outcomes measured included asthma symptoms, need for relief medication (short acting β_2-agonists), spirometry, exhaled NO, bronchial hyper-reactivity, exhaled breath condensate and induced sputum for inflammatory markers.

Preliminary data analyses performed to date indicate: (1) The 2-hour exposure in Oxford Street led to a small and statistically insignificant, change in asthma symptom scores. (2) The exposure resulted in up to ~7% reduction in $FEV_{1,}$ statistically significant at almost all time points during and 6 hours following the exposure. Reduction in FVC was also observed but was not always statistically significant at all time points of measure. (3) The exposure led to increased oxidative stress and pulmonary inflammation, with evidence for this found in exhaled breath condensate pH, sputum neutrophils, interleukin-8, and myeloperoxidase. (4) The effects on lung function and exhaled condensate pH were stronger in moderate asthmatics than in mild asthmatics. The natural day-to-day variations in ambient concentration of DE-related pollutants enabled exposure-response analyses, which are currently in process. The decline in lung function showed the strongest relationship with levels of elemental carbon and ultrafine particles and, to a lesser extent, NO_2 and $PM_{2.5}$. Some of inflammatory and oxidative stress showed similar trends, providing a possible explanation of the mechanism for the observed lung function reductions.

Atmospheric Transformations of Diesel Emissions

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The overall objective of this study is to investigate photochemical transformations of diesel emissions in the atmosphere. The specific aims are: (1) to characterize the gas- and particle-phase products of atmospheric transformations of diesel emissions under the influence of sunlight, ozone, hydroxyl radicals, and nitrate radicals (in the dark); and (2) to explore the changes in biological activity of diesel exhaust before and after the atmospheric transformations take place. The project is being executed with the aid of the EUPHORE simulation chamber in Valencia, Spain, which is currently the largest (~200 m^3) and the best equipped outdoor simulation chamber in the world, allowing investigation of atmospheric transformation processes under realistic ambient conditions (dilution in the range of 1:300). Diesel exhaust is generated on-site using a light-duty diesel engine and a dynamometer system, which is equipped with the Horiba continuous gas analyzer. A modern diesel engine (i.e. a common rail direct injection, turbocharged, intercooled engine) was obtained from Ford Motor Company and has been mounted on the dynamometer. The first series of experiments was carried out in January 2005 (winter campaign) and the second in May 2005 (summer campaign). A diesel fuel that most closely matched what is currently used (or will be used in the near future) in most of the United States was employed (47 ppm sulfur and 15% aromatic content). The test matrix provided experiments that examine the effects of aging and NO_3 radical (obtained from N_2O_5 decomposition) reactions in the dark and photooxidation and OH radical reactions in the light on the composition of diesel exhaust. To determine the particle size, number and volume concentrations the Scanning Mobility Particle Sizer (SMPS) was used and the particle mass was continuously monitored using TEOM. NOx and NOy species were monitored using chemiluminescence and Fourier Transfer Infrared (FTIR) instruments. The semi-volatile and particle-associated organic compounds (SVOC) were collected from the chamber at the end of the exposures, using an XAD coated annular denuder followed by a Teflon-impregnated glass fiber (TIGF) filter and XAD cartridge. The samples for toxicity evaluation were collected using 8 x 10-inch Teflon filters followed by two XAD cartridges. In addition, canister samples were collected for volatile organic compounds (VOC) analysis, 2,4-dinitrophenylhydrazine (DNPH) impregnated cartridges for carbonyl compound analysis and diesel particles on quartz fiber filters for organic and elemental carbon (OC/EC) analysis. This poster will present the results of chemical analyses and toxicity testing of the samples obtained during winter and summer campaigns.

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Speakers, Chairs, and Discussants

Principal Investigators and Poster Presenters

* Study not funded by HEI.
† Poster presenter if not the Principal Investigator.

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