



HEALTH
EFFECTS
INSTITUTE

ANNUAL CONFERENCE 2008
Program and Abstracts

April 27–29, 2008

Sheraton Society Hill Hotel
Philadelphia, Pennsylvania

One Dock Street
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HEALTH EFFECTS INSTITUTE

2008 Annual Conference

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Philadelphia, PA

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HEI Annual Conference 2008

Sunday, April 27, 2008

11:30 PM Lunch

1:00 PM **Opening** *Daniel Greenbaum*, Health Effects Institute

1:10–3:15 PM **Biofuels on the Rise**

Chairs: *Melvyn Branch*, University of Colorado and HEI Research Committee; and *Kent Hoekman*, Desert Research Institute

Biofuels can offer advantages over conventional fuels for reducing dependence on petroleum and reducing greenhouse gas emissions. However, the potential environmental and health impacts of producing and using biofuels need to be considered. This session will provide an overview of biofuels, current trends in production and utilization, life-cycle analyses, and characterization of biofuel emissions and their effect on air quality. Ethanol will be used as an example to illustrate the issues surrounding technology, feedstock, and environmental impacts.

1:10 **Overview of Biofuels**
Kent Hoekman

1:35 **National Programs for Renewable Fuels**
Paul Argyropoulos, US Environmental Protection Agency

1:55 **Emissions from Ethanol and Biodiesel Fuels**

1:55 *Douglas Lawson*, National Renewable Energy Laboratory

2:15 *David Kittelson*, University of Minnesota

2:35 **Life-Cycle Assessment of Ethanol Fuel**
Daniel Kammen, University of California, Berkeley

3:00 **General Discussion**

3:15–3:30 PM Break

3:30–5:30 PM **Poster Session 1**

HEI research on air toxics, particulate matter, and diesel exhaust will be presented along with complementary research supported by other organizations.

6:00 PM **Reception and Dinner**

Monday, April 28, 2008

8:00–9:30 AM Progress at HEI

Chairs: *Homer Boushey*, University of California, San Francisco, and HEI Review Committee; and *Mark Utell*, University of Rochester and HEI Research Committee

Two recipients of the 2007 Walter A. Rosenblith New Investigator Award will be introduced. A recently completed and important HEI-funded study (the American Cancer Society extended follow-up study) will be presented, followed by progress on two HEI activities: the Advanced Collaborative Emissions Study and the Traffic-Related Air Pollution Literature Review.

8:00 Walter A. Rosenblith New Investigator Award: 2007 Recipients

Annemoon van Erp, Health Effects Institute

Charles Stanier, University of Iowa

Yifang Zhu, Texas A&M University–Kingsville

8:15 Extended Follow-Up and Spatial Analyses of the American Cancer Society Study Linking Particulate Air Pollution and Mortality

8:15 Research Findings

Daniel Krewski, University of Ottawa, Canada

8:40 HEI Review Committee Comments

Ben Armstrong, London School of Hygiene and Tropical Medicine, UK, and HEI Review Committee

8:55 Advanced Collaborative Emissions Study: Phase 1

Chris Tennant, Coordinating Research Council

9:15 Critical Review of the Studies of the Health Effects of Traffic-Related Air Pollution

Ira Tager, University of California, Berkeley, and HEI Research Committee

9:30–9:50 AM Break

9:50–11:45 AM From Sound Science to Sound Decisions

Chairs: *Sverre Vedal*, University of Washington; and *Robert O'Keefe*, Health Effects Institute

This session will cover recent developments in how governments translate science on air pollution and health into regulating air quality. Topics include the US Environmental Protection Agency's revised process for reviewing the National Ambient Air Quality Standards using the NO₂ Integrated Science Assessment as an example; and new policy efforts in India and in California.

9:50 Introduction

Sverre Vedal

9:55 EPA's Revised NAAQS Process and Integrated Assessment of NO₂

Ila Cote, US Environmental Protection Agency

10:20 The Clean Air Science Advisory Committee's Perspective on the NAAQS Process

Jonathan Samet, Johns Hopkins University

10:40 National Ambient Air Quality Standards in India

B Sengupta, Central Pollution Control Board, Delhi, India

- 11:05** **Regulation of Ports and Goods Movements in California**
Mike Scheible – California Air Resources Board
- 11:30** **General Discussion**
- 11:45 AM–1:30 PM** **Lunch with Keynote Speaker**
Kathleen McGinty, Secretary, Pennsylvania Department of Environmental Protection
- 1:30–3:15 PM** **Poster Session 2**
HEI research on air toxics, particulate matter, and diesel exhaust will be presented along with complementary research supported by other organizations.
- 3:15–3:30 PM** **Break**
- 3:30–6:00 PM** **Air Pollution and Cardiovascular Disease: Mechanisms and Susceptibility**
Chairs: *Stephanie London*, National Institute for Environmental Health Sciences and HEI Review Committee; and *William Rom*, New York University and HEI Review Committee
- Session topics include possible mechanisms that could explain links between air pollution exposure and development of cardiovascular disease and cardiac events, including changes in gene expression not explained by genetic variations (epigenetic) and the role of susceptibility factors. Studies with people and animal models will be discussed.
- 3:30** **Introduction**
Stephanie London
- 3:35** **Mechanisms Linking PM Exposure and the Development of Cardiovascular Disease and Cardiac Events**
Murray Mittleman, Beth Israel Deaconess Medical Center
- 4:10** **Epigenetic Changes in Response to Exposure to Air Pollution**
Andrea Baccarelli, Università degli Studi di Milano, Italy
- 4:40** **Associations Between PM, Traffic, and the Development of Cardiovascular Disease**
Barbara Hoffmann, University Hospital of Essen, Germany
- 5:15** **Cardiovascular Effects in Animal Models Exposed to Defined Sources**
Matthew Campen, Lovelace Respiratory Research Institute
- 5:45** **General Discussion**
- 6:00 PM** **Free Evening**

Tuesday, April 29, 2008

8:30–11:30 AM Examining Exposure to Air Toxics in Potential Hot Spots

Chairs: *Bert Brunekreef*, University of Utrecht, the Netherlands, and HEI Review Committee; and *Brian Leaderer*, Yale University

One strategy for understanding possible health effects from exposure to air toxics is to study populations living in areas with relatively high concentrations of these pollutants (hot spots). However, before studies to evaluate health risks at environmentally relevant exposure concentrations can begin, studies to confirm actual hot spots are needed. Speakers will discuss results from HEI studies and others about whether concentrations in several possible hot spots are high enough to conduct health-based studies. They will present data from neighborhoods near busy road systems and those near both roads and industrial areas.

8:30 Introduction

Bert Brunekreef

8:40 Assessing Personal Exposure to Air Toxics in Camden, New Jersey

Paul Lioy, Environmental and Occupational Health Sciences Institute

9:10 Multiple Air Toxics Exposure Study (MATES) III

Jean Ospital, South Coast Air Quality Management District

9:40 Air Toxics Exposure to Vehicular Emissions at a US Border Crossing

John Spengler, Harvard School of Public Health

10:10–10:30 AM Break

10:30 Detroit Exposure and Aerosol Research Study (DEARS)

Ronald Williams, US Environmental Protection Agency

11:00 Concluding Remarks

Brian Leaderer

11:30 AM–12:30 PM Boxed Lunch

12:30–3:00 PM Time-Series Studies: What Do They Contribute?

Chairs: *Ross Anderson*, St. George's Hospital, UK, and HEI Review Committee; and *Ben Armstrong*, London School of Hygiene and Tropical Medicine, UK, and HEI Review Committee

Time-series studies of the health effects of short-term exposure to air pollution have been a central part of the scientific evidence that informs US and international air quality management and regulation. With a focus on HEI-sponsored time-series studies and methodologic research, this session will explore the ongoing role of time-series studies in air pollution science and policy. Speakers will discuss the robustness of time-series study estimates, regional variability in results, limitations of current statistical methods, new evidence at the high end of the concentration–response function, and consistency in evidence from studies of long- and short-term exposures to particulate matter and ozone.

12:30 Introduction

Ross Anderson

12:40 What Do Time-Series Studies Tell Us About the Health Effects of Air Pollution?

Ari Rabl, École des Mines, France

- 1:10** **How Certain Is the Evidence? Results from *Air Pollution and Health: A Combined European and North American Approach (APHENA)***
Francesca Dominici, Johns Hopkins University
- 1:35** **New Science from HEI's Public Health and Air Pollution in Asia (PAPA) Program**
- 1:35** **Overview of Coordinated and Combined Analyses**
Chit Ming Wong, University of Hong Kong, China
- 1:55** **Results at Temperature Extremes**
Zhengmin Qian, Penn State College of Medicine
- 2:15** **New Evidence at the High End of the Concentration-Response Function: Results and Implications**
Bart Ostro, California Environmental Protection Agency
- 2:35** **Discussants and General Discussion**
Sverre Vedal and Ben Armstrong

3:00 PM **Conference Adjourns**

PLEASE NOTE: WITH THE SPEAKER'S PERMISSION, PRESENTATION SLIDES WILL BE POSTED AT www.healtheffects.org/annual.htm AFTER THE CONFERENCE.

POSTER SESSION 1

Sunday, April 27, 3:30–5:30

ACCOUNTABILITY STUDIES

HEI's accountability research program was designed to evaluate how regulations and other actions to improve air quality might impact public health. The program currently comprises eight studies: one has just started, four are ongoing, and three were recently completed. A ninth study that evaluated complex changes associated with the reunification in Germany was completed last year and is currently in press. The majority of HEI-funded studies are investigating interventions that are typically implemented over a relatively short period of time. Several studies are evaluating changes that promote cleaner fuels or combustion technology, such as a ban on the sale of coal, replacing old wood stoves with cleaner ones, and decreasing sulfur content in fuel.

HEI is also supporting research and development of methods for an especially challenging field of interest — evaluating which changes in air quality may be associated with regulations that are being implemented incrementally over extended periods of time. For example, HEI is funding a study to evaluate changes made in response to Title IV of the Clean Air Act Amendments of 1990, which is aimed at reducing SO₂ emissions from power plants. Other studies are evaluating measures to reduce traffic congestion or traffic-related air pollution, such as the congestion charging scheme in London. Two projects are investigating the health effects of short-term changes in air quality surrounding the Olympic Games in Atlanta and Beijing.

Conducting accountability studies in the United States would be facilitated by nationwide efforts to track changes in public health. The Centers for Disease Control and Prevention (CDC) will present a poster about the Environmental Public Health Tracking program.

Interventions Aimed at Introducing Cleaner Fuels and Advanced Combustion Technology

Dr. Dockery is evaluating how a ban on coal sales in 11 cities in Ireland in the 1990s may have affected air pollutant concentrations, mortality rates, and hospital admission rates (abstract not available). **Dr. Noonan** is investigating how implementing a community-wide replacement of “dirty” wood stoves in rural Montana may affect ambient particulate matter (PM) levels and respiratory symptoms in children. **Dr. CM Wong** is extending analyses of existing data to evaluate the short- and long-term effects of the 1990 Hong Kong regulation that limited sulfur content in fuel to 0.5%. By applying spatial variation models to existing pollutant and mortality data collected by government agencies, he is evaluating how changes in the mixture of air pollutants (sulfur dioxide, nitrogen dioxide, ozone, PM, and the chemical composition of PM) may affect mortality.

Dr. Morgenstern is evaluating the possible influence 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 is on how implementing the regulation has affected emissions and how those changes relate to improved air quality.

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 Community Wood Stove Changeout on Ambient and Indoor Air: Interim Results. CW Noonan, TJ Ward, K Hooper, W Navidi, and L Sheppard

Impact of the 1990 Hong Kong Legislation for Restriction on Sulfur Content in Fuel: An Approach Modeling the Relationship Between Mortality and Air Pollution Taking Account of Past Exposures. CM Wong, A Rabl, TQ Thach, YK Chau, HK Lai, KP Chan, BC Cowling, TH Lam, SM McGhee, HR Anderson, and AJ Hedley

Interventions Aimed at Reducing Traffic Congestion and Emissions

Two studies led by **Dr. Kelly** take advantage of efforts to decrease traffic in Central London. One study is comparing air pollutant concentrations and PM toxicity before and after the introduction of a congestion charging scheme implemented by Transport for London in 2003. His other study is assessing the impact of designating Greater London as a Low Emission Zone (LEZ), a plan that will restrict entry for the oldest and most polluting vehicles. Dr. Kelly recently finished collecting baseline air quality measurements in anticipation of the LEZ being implemented in February, 2008.

Dr. Peel's study expanded upon an earlier one that had assessed how measures to reduce traffic congestion during the 1996 Summer Olympic Games in Atlanta, Georgia, affected children's asthma. Dr. Peel subsequently evaluated cardiorespiratory health outcomes, including emergency department visits and arrhythmic events, before, during, and after the Olympics. **Dr. J Zhang** will be evaluating respiratory function and vascular endpoints in a group of medical students in Beijing, China, during the weeks of reduced air pollution surrounding the 2008 Olympic Games and comparing them with periods before and after the games when higher pollutant levels are expected.

Congestion Charging Scheme in London: Assessing Its Impact on Air Quality. 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

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

The Beijing HEART Study — Health Effects of Air Pollution Reduction Trial. J Zhang, T Zhu, H Kipen, G Wang, W Huang, D Rich, P Zhu, Y Wang, M Hu, M Shao, X Tang, S-E Lu, P Ohman-Strikland, S Diehl, X Pan, X Guo, and D Thomas

Environmental Public Health Tracking

The Centers for Disease Control and Prevention, in collaboration with state agencies and the US Environmental Protection Agency, has initiated an Environmental Public Health Tracking (EPHT) program to monitor the health effects of environmental pollution across the United States (presented by **Dr. J Qualters**). This effort could be important for future accountability studies at the national, regional, and local levels, as noted in the HEI Strategic Plan for 2005–2010. In January 2008, the CDC, EPA, and HEI held a workshop that brought together representatives of state and national public health and environmental agencies with academic researchers from the US and Europe to further define indicators of health effects of air pollution suitable for public health tracking.

***Leveraging Environmental Public Health Tracking for Chronic Disease Prevention.** J Qualters, A Lekachvili, A Charleston, and S Rezai

ACCESS TO AIR QUALITY AND EXPOSURE DATA

Several initiatives are providing air quality, exposure, and health-indicator data to the research community and other interested parties. In the past, HEI has supported two projects to facilitate access to data sets collected by government agencies or research groups. First, the internet-based Health and Air Pollution Surveillance System (iHAPSS) made available data

* Study not funded by HEI.

and software from the *National Morbidity, Mortality, and Air Pollution Study (NMMAPS)*. Second, the HEI Air Quality database, created for the *National Particle Components Toxicity (NPACT) Initiative* (see page 13) provides access to data on PM components across the United States. A third, ongoing project (**Dr. Pun**) is creating a web-accessible database to provide access to data from the *Relationships of Indoor, Outdoor, and Personal Air (RIOPA)* study, which was funded jointly by HEI and the Mickey Leland National Urban Air Toxics Research Center.

Development of a Web-Accessible Relational Database for Air Toxics and PM_{2.5} Based on the RIOPA Study. B Pun, C Seigneur, S-Y Chen, and M Sze

ENGINE EMISSIONS AND THEIR EFFECTS ON HEALTH

HEI is funding a range of studies to evaluate emissions from diesel and gasoline engines by characterizing the emissions components and the effects on health endpoints *in vitro* and *in vivo*.

Last year, HEI and the Coordinating Research Council (CRC) moved forward with the *Advanced Collaborative Emissions Study (ACES)*: a cooperative, multiparty effort to characterize emissions and assess the possible health impacts of the new, advanced heavy-duty diesel-engine and after-treatment systems introduced into the market from 2007 through 2010. Phases 1 and 2 of ACES include extensive characterization of emissions from engines and after-treatment systems designed to comply with the 2007 and 2010 regulations. With oversight from CRC, a team led by **Dr. Khalek** is characterizing emissions from four 2007-compliant diesel engines.

In Phase 3, starting in December, 2008, investigators will conduct a long-term inhalation bioassay with rats and a shorter-term study with mice. One of the four diesel engines tested in Phase 1 will be installed in a facility (currently under construction) specially designed for emissions generation and animal exposures. A team led by **Dr. Mauderly** will conduct a core 24-month inhalation bioassay with rats following a protocol similar to the one used for the US National Toxicology Program bioassay.

In addition to assessing the possible carcinogenicity of whole diesel exhaust, the chronic bioassay would provide information on chronic toxicity, *in vivo* mutagenicity, and non-cancer health endpoints that have been associated with exposure to diesel exhaust by examining subsets of rats at different times during exposure. In addition, mice will be evaluated for non-cancer endpoints in a concurrent 3-month inhalation study.

Update on Phase 1 of the Advanced Collaborative Emissions Study (ACES-1). IA Khalek, TL Bougher, and PM Merritt

Status of ACES Phase 3: Chronic Inhalation Bioassay. J Mauderly, D Griego, J McDonald, M Jorgensen, and G Rees

HEI is also funding a study to evaluate how diesel exhaust and NO₂ may exacerbate asthma symptoms and allergic responses. **Drs. Effros and Riedl** are assessing whether inflammatory and immunologic changes are observed in the airways of volunteers with allergic asthma when exposed to diesel exhaust (this study was formerly led by Dr. Diaz-Sanchez and the late Dr. Gong). **Dr. Laskin** is conducting a pilot study to determine whether aged mice exhibit increased sensitivity to inhaled diesel exhaust and, if so, whether the response is associated with reduced expression of TNF- α and antioxidants in the lung. **Dr. SS Wong** is testing the hypothesis that exposing a lung epithelial cell line to diesel exhaust particles inhibits neutral endopeptidase, an enzyme that breaks down several neuropeptides involved in cell proliferation and differentiation.

Exacerbation of Allergic Inflammation in the Lower Respiratory Tract by Diesel Exhaust. [RM Effros](#), [MA Riedl](#), D Diaz-Sanchez, H Gong Jr. (deceased), WS Linn, KW Clark, JW Miller, and DR Cocker

Increased Sensitivity of Elderly Mice to Inhaled Diesel Exhaust. [DL Laskin](#), KJ Patel, RJ Laumbach, S Ridgely, BJ Turpin, G Mainelis, and VR Sunil

Diesel Exhaust Particles–Induced Acute Loss of Respiratory Neutral Endopeptidase. [SS Wong](#), NN Sun, HB Miller, ML Witten, and JL Burgess

A key issue in trying to evaluate the effects of air pollutants is understanding the chemical transformation that pollutants undergo in the atmosphere. Such transformations can yield new chemical species that may affect the reactivity of pollutants and their fate when inhaled. In addition, improvements in engines and after-treatment technology, although reducing overall emissions, may change the characteristics of the exhaust. HEI is funding several studies to examine the properties of emissions from different sources.

Dr. Zielinska has evaluated the chemical and physical changes of the components of exhaust from a recent light-duty diesel engine and has examined the toxicity of these transformed products in vivo and in vitro. **Dr. Baum** is investigating 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 is developing analytic methods to detect low levels of these compounds and will use these methods to measure ambient levels and emission rates.

Significance of Highly Toxic Secondary Emissions from On-Road Vehicles. J Stihle, D Key, JA Moss, and [MM Baum](#)

Atmospheric Transformation of Diesel Emissions. [B Zielinska](#), JD McDonald, S Samy, and J Seagrave

EXPOSURE ASSESSMENT AND MODELING

To predict personal exposure more accurately, it is important to determine the components of PM and other compounds to which people are exposed in a variety of settings. However, it is challenging to measure the low concentrations of the complex array of components in the pollution mixture. A second challenge is to obtain accurate exposure estimates for both individuals and large populations.

Dr. Levy, a 2005 recipient of the HEI's Walter A. Rosenblith New Investigator Award, is extending geographic information system (GIS)–based methods to 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. **Dr. Paciorek**, a 2006 recipient of the Walter A. Rosenblith New Investigator Award, is estimating PM_{2.5} concentrations by integrating satellite and ground monitoring data.

Two 2007 recipients of the Walter A. Rosenblith New Investigator Award are (1) constructing an exposure estimation model based on several existing models to predict ultrafine particle formation from secondary photochemical processes and from vehicle exhaust in large urban areas (**Dr. Stanier**); and (2) measuring ultrafine particle levels in classrooms and in school buses under a variety of conditions: different engine after-treatment devices, traffic density, and ventilation (**Dr. Zhu**).

Assessing Indoor and Outdoor Residential PM_{2.5} Source Contributions Using GIS and Non-Negative Matrix Factorization. JE Clougherty, EA Houseman, and [JI Levy](#)

Assessing the Utility of Satellite Aerosol Optical Depth Data for Retrospective Estimation of Monthly PM_{2.5} Concentrations in the Eastern United States. [CJ Paciorek](#) and Y Liu

Development of a Personal Exposure Aerosol Screening Model (PEASM) for Size-Resolved Urban Aerosols: Model Architecture and Study Objectives. [CO Stanier](#) and S-R Lee

Assessing Children's Exposure to Ultrafine Particles from Vehicular Emissions. [Y Zhu](#) and Q Zhang

EFFECTS OF PARTICULATE MATTER COMPONENTS

An important question regarding health effects of PM is whether some components are more harmful to health than others and should therefore be the focus of future regulations. HEI has put in place the NPACT Initiative — a program of systematic, high-quality research that is supported by a broad range of government, industry, and other stakeholders — to answer key aspects of this question in time to inform future PM regulatory decisions. The NPACT Initiative comprises three studies.

Two of the teams will conduct integrated toxicologic and epidemiologic studies in a number of cities across the United States where the composition of PM differs. **Drs. Vedal** and **Mauderly** are leading one team studying animals and human populations to focus on long-term cardiovascular effects of exposure to components of fine PM and gaseous pollutants from defined sources. **Dr. Lippmann's** team is evaluating short- and long-term cardiovascular effects of exposure to gaseous pollutants and components of fine PM; they are conducting coordinated toxicologic studies with animals exposed to concentrated ambient particles from various US locations and epidemiologic studies of human populations. A third study by **Dr. Bell**, a 2004 recipient of HEI's Walter A. Rosenblith New Investigator Award, is developing analytic methods to evaluate the effects of various components of the PM mixture on cause-specific mortality in time-series studies. She is using data from the HEI-funded *National Morbidity, Mortality, and Air Pollution Study (NMMAPS)* and other sources.

Seasonal and Regional Short-Term Effects of Fine Particles on Hospital Admissions in 202 US Counties. [ML Bell](#), K Ebisu, RD Peng, JM Samet, SL Zeger, and F Dominici

Characteristics of PM Associated with Health Effects. [M Lippmann](#), LC Chen, T Gordon, K Ito, GD Thurston, and A Nadas

Integrated Epidemiologic and Toxicologic Cardiovascular Studies to Identify Toxic Components and Sources of Fine Particulate Matter. [S Vedal](#), J Kaufman, T Larson, D Wilton, P Sampson, L Sheppard, C Simpson, J Mauderly, M Campen, and J McDonald

POSTER SESSION 2

Monday, April 28, 1:30–3:15

MOBILE-SOURCE AIR TOXICS

Air toxics are a diverse group of air pollutants that, with sufficient exposure, are known or suspected to cause adverse health effects, including cancer, changes in the development of organs or tissues, and damage to the immune, neurologic, reproductive, and respiratory systems.

Possible Hot Spots of MSAT Exposure

Evaluating the magnitude of a population's exposure is a crucial step in the process of assessing risks. However, many of the predictions of health risks are based on modeled estimates of exposure rather than ambient measurements. HEI funded five research projects to measure concentrations of air toxics in areas believed to have high levels because both industrial and mobile sources of these pollutants are present; all have been completed and are under review.

The five studies measured personal, occupational, and residential exposure of populations working or living in areas that are thought to be hot spots. Two studies that were completed last year evaluated locations near truck terminals or near heavily traveled roadways with mixed traffic or heavy-duty trucks. Three studies that were completed recently evaluated areas with heavy stop-and-go truck and car traffic (**Dr. Spengler**), areas with a mix of vehicular and light industrial pollution (**Dr. Lioy**), and personal and microenvironment exposures in three cities with different levels of traffic-associated air pollution (**Dr. Harrison**).

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

Personal Exposures to and Spatial Variations of Air Toxics in a “Hot Spot” in Camden, New Jersey. [PJ Lioy](#), Z Fan, J Zhang, P Georgopoulos, SW Wang, PA Ohman, JL Held, and LJ Bonanno

Spatial Patterns of Particle-Bound PAHs and Fine Particulate in the Neighborhood of West Buffalo Adjacent to a Major Border Crossing. S Melly, J Vallarino, J Lwebuga-Mukasa, S Chillrud, and [JD Spengler](#)

In addition, HEI has invited posters from other exposure-assessment studies in possible hot spot areas. These include measurements in large urban areas, such as Houston (**Dr. Morandi**), Detroit and Windsor (**Dr. J. Brook**), and Southern California (**Dr. Ospital**), as well as in a heavily polluted area in the Czech Republic (**Dr. Šrám**).

* **Houston Exposure to Air Toxics Study.** [M Morandi](#), T Stock, C Beskid, L Shirnamé-Moré, and E Hendler

* **Using an Advanced Mobile Lab to Characterize Urban Spatial Patterns, Local Sources, and Hotspots.** [J Brook](#), C Mihele, G Lu, J Narayan, I Xu, and A Wheeler

* **Multiple Air Toxics Exposure Studies in the South Coast Air Basin of Metropolitan Los Angeles.** [J Ospital](#), J Cassmassi, T Chico, L Pham, B-M Kim, A Katzenstein, S Wilson, and P Fine .

* **European Hot Spot of Air Pollution for PM_{2.5} and B[a]P: Ostrava, Czech Republic.** [RJ Šrám](#)

* Study not funded by HEI.

Mutagenicity of 1,3-Butadiene

An experimental study is extending results from earlier HEI-funded research by identifying the relative mutagenicity of several metabolites of 1,3-butadiene. **Dr. Walker** is measuring levels of 1,2:3,4-diepoxybutane, which is formed in mice and rats exposed to butadiene by inhalation. He is measuring the metabolite directly (in the blood) and indirectly (through the formation of adducts with DNA and protein, and by identifying specific types of mutations).

Induction of 1,2:3,4-Diepoxybutane-Specific Hemoglobin and DNA Adducts in Mice and Rats Exposed to 1,3-Butadiene. N Tretyakova, M Goggin, NI Georgieva, G Boysen, PB Upton, JA Swenberg, and VE Walker

MECHANISMS OF TOXICITY OF PARTICULATE MATTER

Several ongoing studies are examining the pathophysiologic effects of exposure to particles in different biological systems — in particular, the cardiovascular system.

Dr. Nurkiewicz, a 2005 recipient of HEI's Walter A. Rosenblith New Investigator Award, is studying the mechanism by which exposure to PM contributes to increased cardiovascular disease. He is assessing the effects of inhaled fine and ultrafine titanium dioxide particles on systemic microvascular circulation in rats. **Dr. Schulz** conducted a pilot study with mice to compare the systemic cardiovascular effects of ultrafine carbon particles administered by two methods: inhalation and intra-arterial infusion. **Dr. Q. Zhang**, a 2006 recipient of the Walter A. Rosenblith New Investigator Award, is investigating the effects of ambient ultrafine particles (collected on filters) on the formation of reactive oxygen species and on endothelial permeability in apo-E knock-out mice, an animal model for hypercholesterolemia. **Dr. Kendall**, a 2004 recipient of the Walter A. Rosenblith New Investigator Award, is evaluating in vitro the interaction of particles with surfactant proteins in lung fluid.

PM Surface-Lung Interactions: Cell Responses to Modified Particle Surfaces. M Kendall

Microvascular Inflammatory Mechanisms Activated After Inhalation of Ultrafine Particulate Matter. TR Nurkiewicz, DW Porter, AF Hubbs, S Stone, BT Chen, D Frazer, MA Boegehold, and V Castranova

Extrapulmonary Effects of Inhaled Ultrafine Carbon Particles in Mice. T Stöger, D Ettehadieh, S Takenaka, and H Schulz

Activation of Endothelial Cells After Exposure to Ultrafine Particles. Q Zhang, Y Mo, R Wan, N Shah, and DJ Tollerud

INTERNATIONAL EPIDEMIOLOGY

Multicity Time-Series Studies in North America, Latin America, and Europe

Air Pollution and Health: A Combined European and North American Approach (APHENA) is a two-part, time-series study led by **Drs. Katsouyanni** and **Samet** and jointly funded by HEI and the European Commission. The study includes data from 9 Canadian cities, the 32 European cities included in the study *Air Pollution and Health: A European Approach (APHEA)*, and the 90 US cities included in the HEI-funded *National Morbidity, Mortality, and Air Pollution Study (NMMAPS)*. The APHENA investigators have developed new approaches for analyzing multicity time-series data and have explored the spatial variation in relative risks of air pollution.

Dr. Romieu and colleagues are using a common analytic framework to examine the association between daily levels of air pollution and mortality in Mexican, Brazilian, and Chilean cities,

with special attention to the impact of air pollution on infants and young children. This study is also evaluating whether socio-economic status influences the relation between air pollution and mortality.

Air Pollution and Mortality in Latin America: Results from the ESCALA Project (Multi-City Study of Air Pollution and Health Effects in Latin America). N Gouveia, W Junger, A Ponce de Leon, V Miranda, M Hurtado, L Rojas, L Carbajal, G Tzintzun, L Cifuentes, V Strappa, and [I Romieu](#)

Air Pollution And Health: A Combined European and North American Approach (APHENA). [JM Samet](#) and [K Katsouyanni](#).

Time-Series Studies in Asia

The Public Health and Air Pollution in Asia (PAPA) research 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. HEI has funded seven time-series studies in mainland China, Hong Kong, Thailand, and India on the health effects of short-term exposure to air pollution.

The three time-series studies in India (**Dr. Balakrishnan** in Chennai, **Dr. Uma** in Delhi, and **Dr. Kumar** in Ludhiana) focus on the impact of air pollution on mortality from natural causes. These three studies follow a common analysis protocol to facilitate intercity comparisons. The studies in Chennai and Delhi were completed last year, and the Ludhiana study will be completed shortly.

Estimating Short-Term Effects of Air Pollution on Mortality from Time-Series Analysis in Chennai, India. [K Balakrishnan](#), B Ganguli, S Gosh, S Sankar, and V Thanasekaraan

Association of Air Pollution and Mortality in Ludhiana City of India: Preliminary Results of a Time-Series Study. [R Kumar](#), JS Thakur, GPI Singh, HK Parwana, SPS Bhatia, SK Jindal, ML Garg, and S Sharma

Time-Series Study on Air Pollution and Mortality in Delhi, India. [R Uma](#), M Seghal, K Chhabra, GC Kilnani, RC Patnayak, and S Raghvan

City-specific time-series studies in Bangkok, Hong Kong, Shanghai, and Wuhan were completed in 2006. Led by **Dr. C.M. Wong**, these investigators have recently completed a combined analysis across all four cities.

Public Health and Air Pollution in Asia (PAPA): A Multicity Study for Short-Term Effects of Air Pollution on Mortality. [CM Wong](#) on behalf of the PAPA research teams:

Bangkok — [N Vichit-Vadakan](#), N Vajanapoom, and B Ostro

Hong Kong — [CM Wong](#), TQ Thach, PYK Chau, KP Chan, CQ Ou, L Yang, JSM Peiris, GN Thomas, TW Wong, TH Lam, and AJ Hedley

Shanghai — [H Kan](#), B Chen, N Zhao, SJ London, G Song, G Chen, Y Zhang, and L Jiang

Wuhan — [Z Qian](#), HM Lin, CM Bentley, Q He, L Kong, N Yang, S Xu, D Zhou, and W Liu

Air Pollution, Poverty, and Health Studies in Vietnam

The program entitled *Air Pollution, Poverty, and Health in Ho Chi Minh City (HCMC)* is being jointly funded by the Asian Development Bank through its Poverty Reduction Cooperation

Fund, by HEI, and by the HCMC government. The conduct of the studies has been led by an interdisciplinary collaborative working group, which has been refining feasible approaches to assess the health impact of air pollution among poor families in HCMC. The project has two main research components: (1) a hospital-based study to estimate effects of short-term exposure to air pollution on hospital admissions for acute lower respiratory infections (ALRI) in children younger than 5 years, and to compare the magnitude of the effects of air pollution on poor children compared with children who are not poor; and (2) a household-based study to estimate personal exposures to air pollution and to evaluate the association between ambient air pollutant concentrations and personal exposures in poor families and families who are not poor.

The Effects of Short-Term Exposure on Hospital Admissions for Acute Lower Respiratory Infections in Young Children of Ho Chi Minh City. [HEI Collaborative Working Group](#)

The Relationship Between Personal and Ambient Exposures in Ho Chi Minh City. [HEI Collaborative Working Group](#)

Cohort Study in the United States

Dr. Krewski recently completed a study that further evaluated the long-term effects of different pollutant mixtures on mortality for the American Cancer Society Study cohort. The team added an additional 18 years of follow-up data (through 2000); and they conducted additional spatial analyses using multilevel spatial information on pollution and confounding variables and controlling for spatial autocorrelation in the data. Their analyses covered the full nationwide ACS cohort and separate subcohorts for Los Angeles and New York.

Extended Follow-Up and Spatial Analysis of the American Cancer Society Study Linking Particulate Air Pollution and Mortality. [D Krewski](#), M Jerrett, RT Burnett, R Ma, E Hughes, Y Shi, MC Turner, CA Pope III, G Thurston, EE Calle, and MJ Thun

Development of Methods

Dr. Robins is developing new statistical approaches to semiparametric regression that will address the impact of confounding factors on relative risk estimates in time-series and cohort studies of the health effects of air pollution.

A New Approach to Semiparametric Regression. [J Robins](#)

ABSTRACTS

Estimating Short-Term Effects of Air Pollution on Mortality from Time-Series Analysis in Chennai, India

K Balakrishnan, B Ganguli, S Gosh, S Sankar, and V Thanasekaraan

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Background: Few time-series studies have been executed in India for estimating health impacts associated with outdoor air pollution. The study reports results of models developed for time series analysis to estimate short-term effects of criteria air pollutants on mortality in the greater Chennai metropolitan area (located in Southern India). Chennai is one of three sites chosen for the coordinated set of Indian PAPA studies with the other two being conducted in New Delhi and Ludhiana respectively.

Methods: Study design was centered on integrating and analyzing data from two principal retrospective data gathering components viz. collection of daily average environmental levels of criteria air pollutants (PM₁₀, SO₂ and NO_x) and collection of daily mortality data (city wide) for the period 2002 to 2004. Air quality, mortality and meteorological data were obtained from the concerned Governmental Agency that is responsible for routine data collection within Chennai city. Datasets were cleaned according to QA/QC procedures set forth in a common protocol for Indian PAPA investigators.

Results: Of the 8 monitors operated routinely, one monitor failed to meet the site selection criteria. Three of the monitors were located within an industrial hot spot and hence were excluded from the initial model. Data from two individual monitors (Anna Nagar and Vallalar Nagar) were used for generating the core model as these fulfilled all QA/QC requirements. Data from other monitors were also analyzed to describe the range of estimates obtained with single or multiple monitors. Alternative exposure series were developed using available or imputed data from single or combinations of valid monitors for the core analyses using generalized additive models (to address possible over-dispersion). A spatial model was also developed to assign differential exposures for various city zones based on proximity to individual monitors. Limited multi-pollutant analysis that included only PM₁₀ and NO_x from select monitors was performed, as reported SO₂ data was clustered around or below the detection limit on most days. Finally, sensitivity analyses were performed to examine the contributions of model parameters (lags, degrees of freedom, spline fitting choices), inclusion/exclusion of outliers, and inclusion of gases and age /sex stratifications of mortality data.

Conclusions: The results of analyses show that the estimates for effects of PM₁₀ (an approximately 0.4% to 0.6% increase in all-cause mortality per 10 µg/m³ increase in daily exposure) are in the range reported by other on-going PAPA studies and earlier studies reported in North America and Europe (using similar statistical methods). The effect estimate was robust to model specifications. More sophisticated analyses including use of EM algorithms to address missing data and auto-correlation are being undertaken to refine these initial estimates. Data quality issues may however limit development of multi-pollutant models and differential cause specific estimates. Consistency of results obtained using similar methodological approaches between Indian cities and other Asian cities indicate that routinely collected pollutant and mortality data may be reliably used in time-series analyses of air pollution related health impacts. However, significant challenges remain in making clean data readily accessible to environmental health researchers.

Significance of Highly Toxic Secondary Emissions from On-Road Vehicles

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Catalytic converters have played a central role in improving air quality by reducing criteria pollutant exhaust emissions from light duty motor vehicles (LDMVs). Side reactions on the catalyst surface, however, produce secondary (i.e., post-combustion) unregulated emissions such as hydrogen cyanide, nitrous acid, nitrous oxide, and ammonia. These compounds have an adverse impact on human health and the environment. Of particular concern is a class of highly toxic compounds termed (chemically-) *reduced nitrogen compounds* (RNCs) that include hydrogen cyanide (HCN); *N*-nitrosamines (RR'NNO); amines (RR'NR''); hydrazine (H₂NNH₂); methylhydrazine [CH₃(H)NNH₂]; and hydroxylamine (HONH₂); 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, may lead to significant adverse health effects, particularly in high exposure scenarios such as freeway communities, vehicle cabins, and enclosed spaces.

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. Results from our Year II activities include:

- 1) Complete validation of developed analytical methods, including the collection of GC/MS reference data for the relevant RNC condensation products and the validation of a literature *N*-nitrosamine method;
- 2) Development and validation of new analytical approaches for the capture and derivatization of key RNCs and a modified GC/MS method for amine measurement;
- 3) Complete evaluation of efficiency, accuracy, and sensitivity of glass annular denuder and silica cartridge methods for the collection of organic condensation products;
- 4) Design and development of an integrated, on-board instrument suite, along with preliminary measurements using select modules, including both idling stationary vehicle and on-road measurement studies;
- 5) Tunnel and freeway field study planning and site selection.

Seasonal and Regional Short-Term Effects of Fine Particles on Hospital Admissions in 202 US Counties

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Background. Previous work has indicated that the association between airborne particles and risk of adverse health response may differ by region and time of year. The chemical composition of particles also exhibits heterogeneity by location and time period.

Methods. We investigated whether short-term effects of fine particulate matter (PM_{2.5}) on risk for cardiovascular and respiratory hospitalizations among the elderly vary by region and season in 202 U.S. counties for the period 1999 to 2005. We fitted three types of time-series models to test for: (1) consistent effects across the year; (2) different effects by season; and (3) smoothly varying effects throughout the year. We also investigated which chemical components of PM_{2.5} have higher levels for the regions and seasons with higher effect estimates compared to the regions and seasons with lower effect estimates.

Results. We found statistically significant evidence of seasonal and regional variation in effect estimates. For respiratory diseases, effect estimates were highest in winter with a 1.05% (95% posterior interval 0.29, 1.82%) increase in hospitalizations per 10 µg/m³ increase in same day PM_{2.5}. For cardiovascular diseases, estimates were also highest in winter with a 1.49% (1.09, 1.89%) increase in hospitalizations per 10 µg/m³ increase in same day PM_{2.5}, with associations also observed in other seasons. The strongest evidence of a relationship between PM_{2.5} and hospitalizations was in the Northeast for both respiratory and cardiovascular diseases.

Conclusions. Heterogeneity of the short-term effects of PM_{2.5} on hospitalizations may relate to seasonal and regional differences in emissions and particles' chemical constituents. Our results can help guide the development of hypotheses and further epidemiological studies on the toxicity of the particulate matter mixture.

***Using an Advanced Mobile Lab to Characterize Urban Spatial Patterns, Local Sources, and Hotspots**

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Background. Human exposures are influenced by air pollutants that vary on regional, urban and local scales. Specific areas of high emissions often referred to as hotspots, can be a major contributor to the exposure for some members of the population. In many cases these areas have high levels of toxic pollutants associated with primary emissions. Understanding the health effects and risks posed by air pollutant exposure thus requires a relatively detailed characterization of exposure patterns across multiple scales.

Methods. A mobile lab, CRUISER, was developed and deployed to several areas in Canada, as well as Detroit, Michigan, to examine concentration gradients ranging from near roadway conditions and around hotspots to patterns across and downwind of urban areas. For mobile measurements, CRUISER houses fast response, high sensitivity gas analyzers (CO, CO₂, SO₂, O₃, NO, NO₂ and NO_y), photoacoustic black carbon and ultrafine particle counts with 1 min or better time resolution. Also on board are an Aerodyne Aerosol Mass Spectrometer (quadrupole AMS) and an Ionicon Proton Transfer Reaction Mass Spectrometer (PTRMS) for five minute PM_{1.0} speciation and selected VOCs, respectively.

Results. Near source and downwind concentrations were measured for a steel mill, a large container ship at berth and a range of roadways from urban street canyons to upwind and downwind of major highways. Other source-impacted areas captured thus far include an oil refinery, residential wood smoke and a wood processing plant. These data are providing insights on the size of the areas influenced by certain hotspots, the spatial covariance in the pollutant mix on the neighbourhood to urban scale and source apportionment. For example, sulphur dioxide emissions from the ship, as a surrogate for diesel-related air toxics, were found to be impacting neighbourhoods at least 10 km downwind from the port of Vancouver. Investigation of one Detroit steel mill location showed that tracers for gas and particle phase PAHs were approximately ten times higher downwind as compared to upwind and could still be detected several kilometres away.

Conclusions. The cases studied to date demonstrate the extent that local hotspots can impact a given population and the value of using a mobile lab for such purposes. This experience is helping to optimize the design for future mobile measurement campaigns for studying source-specific health effects and improving sub-grid scale information for air quality model emissions and exposure-related applications.

* Study not funded by HEL.

Exacerbation of Allergic Inflammation in the Lower Respiratory Tract by Diesel Exhaust

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Background. Diesel exhaust (DE) is an important contributor to ambient particulate matter (PM). Ambient PM exposure increases risk of respiratory illness, but mechanisms are not well understood. One possible mechanism is potentiation of response to respiratory allergens by coexisting diesel PM, which has been observed in the nose. We are currently attempting to demonstrate it in the lower respiratory tract, by exposing asthmatic volunteers to dilute diesel exhaust and then challenging them with inhaled allergen.

Methods. In the current Phase 2, volunteers with documented asthma and sensitivity to cat allergen undergo controlled 2-hr chamber exposures with intermittent exercise to 1) DE from an idling truck diluted by filtered air to $\sim 100 \mu\text{g}/\text{m}^3$ particulate matter and ~ 400 ppb NO_2 ; 2) 400 ppb NO_2 in filtered air, representing the most toxic gas component of diesel exhaust; and 3) filtered-air (FA) control. Immunologic responses are documented by assays of peripheral blood and induced sputum. Clinical responses are documented by lung function tests, vital signs, symptom questionnaires, exhaled NO and CO, and post-exposure challenge with inhaled cat allergen, individually standardized. In the previous Phase 1, the protocol was similar, with a methacholine (nonspecific airway reactivity) challenge instead of cat allergen.

Interim Results. Seven of a projected 15 cat-sensitive asthmatic volunteers have completed their exposure studies. In those exposures, particle mass concentrations from filter samples averaged $143 \mu\text{g}/\text{m}^3$ in DE, 25 in NO_2 , and 24 in FA. NO_2 concentrations averaged 355, 387, and 20 ppb respectively. Total ultrafine+fine particle concentrations measured in DE by scanning mobility particle sizer (SMPS) were close to the target, $100 \mu\text{g}/\text{m}^3$. Thus, excess mass on filters presumably was large particles generated by subjects and exercise equipment. Frozen blood and sputum samples are in storage until completion of the exposures, when all will be assayed in one batch. Interim analysis of clinical response data showed no significant differences between atmospheres in forced expiratory lung function (FEV_1), specific airway resistance, blood pressure, arterial O_2 saturation (by pulse oximeter), exhaled NO, total symptom intensity, or FEV_1 response to cat allergen. A trend toward increasing exhaled CO after DE exposures (which had CO concentrations averaging >2 ppm, versus <1 ppm otherwise) did not attain statistical significance.

Interim Conclusions. Results so far appear consistent with Phase 1 (D. Diaz-Sanchez, 2007 HEI Conference presentation) in showing little immunologic or clinical response to $100 \mu\text{g}/\text{m}^3$ diesel PM. Analysis of pooled data from both phases (and perhaps eventually from similar experiments elsewhere) will increase statistical power to detect subtle responses.

Future Plans. Perform exposure studies on additional cat-sensitive volunteers. Perform blood and sputum assays on all Phase 2 subjects. Statistically analyze results for Phase 2, and for combined Phase 2 and Phase 1.

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

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Objectives. The overall aim is 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.

The specific goals of research are:

- To use personal monitoring of non-smoking volunteers with a range of residential locations and exposure to non-traffic sources to assess daily exposures.
- To determine microenvironment concentrations of a range of air toxic substances (volatile organic compounds [VOC] including 1,3-butadiene and polycyclic aromatic hydrocarbons [PAH]) taking account of spatial and temporal variations and hotspots.
- 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.
- To produce a scheme for categorising exposure (by compound) according to location of residence, other lifestyle and exposure factors (e.g. environmental tobacco smoke [ETS]) for use in design of case control and ecological studies of cancer incidence.

Methods. Personal exposure measurements were made 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. During the period when personal exposures were being measured, there was 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, pubs, restaurants, libraries, car parks, train stations. Volunteers recorded their activities each day in an activity diary, This information was used to reconstruct exposures to air toxics based upon the location information and time activity records. VOC collected in tubes packed with Tenax GR and Carbotrap and 1,3-butadiene tubes packed with Carbopack B and Carbosieve SIII were analysed by means of a thermal desorber interfaced with a GC/MS. Particle phase PAH collected onto a quartz fibre filter were extracted with solvent, purified and concentrated prior to being analysed by GC/MS.

Summary of the Results. The variability of VOC and PAH 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.

Personal exposures were generally within the expected range of values and remained consistently higher in suburban and urban volunteers compared with rural ones for most of the compounds studied. It appears that personal exposure levels are in reasonable agreement with "home" and "work" concentrations. As well, personal exposure concentration remained consistently higher during days of the week associated with increased vehicle use and ETS exposure. Four different approaches have been taken to modelling personal exposure, using 75% of the measured personal exposure dataset to develop the models and 25% as an independent check on the model performance.

Interpretation and Conclusion. The best personal exposure model is able to account for about 50% of the variance in measured personal exposure, based upon measured microenvironment concentrations and lifestyle factors.

The Effects of Short-Term Exposure on Hospital Admissions for Acute Lower Respiratory Infections in Young Children of Ho Chi Minh City (HCMC)

HEI Collaborative Working Group on Air Pollution, Poverty, and Public Health in Ho Chi Minh City

In cooperation with an initiative of the Asian Development Bank, an interdisciplinary team of local and international experts is assessing the health effects of air pollution among the poor in HCMC. The project has two complementary components – a hospital-based study (discussed here) and a household-based study. In the hospital study, we estimate the effect of short-term exposure to air pollution on hospital admissions for acute lower respiratory infections (ALRI) in young children in HCMC, and compare the magnitude of the effect of air pollution on poor children vs. other children.

METHODS: We used routinely collected data on air quality, hospital admissions, and socio-economic position (SEP) from 2003 – 2005 to estimate the effect of short-term exposure to air pollution on hospital admissions for ALRI in young children (<5 years). Admissions for pneumonia, bronchiolitis, and bronchitis in children less than five years of age were extracted from computerized records of Children's Hospitals 1 and 2. HCMC Environmental Protection Agency provided daily, city-level exposure estimates of PM₁₀, O₃, NO₂, and SO₂. Meteorological information was also collected. Analysis was conducted using case-crossover and time-series methodologies. Effect modification by SEP was assessed in the case crossover analysis using individual and group level indicators of SEP.

RESULTS: From 2003-2005, there were a total of 28,085 admissions. Individual financial data were linked to over 93% of these of these admissions. City-wide, daily average pollutant values were generated for the same period. Large seasonal differences in admission patterns and pollution levels were observed. Around 60% of ALRI admissions occur during the rainy season. In contrast, the highest pollutant concentrations are observed in the dry season. In order to control for these seasonal differences in admissions and pollution levels, analyses were stratified by (rather than simply adjusted for) season. When this was done, the results differed markedly between the rainy and dry seasons.

In general, positive associations between PM₁₀ and Ozone and increased ALRI admissions were observed in the dry season, and negative associations were observed in the rainy season. Results were consistent across time series and case crossover analyses. Ozone effects were consistently higher than PM effects. Percent increases for the most severe forms of ALRI tended to be larger, perhaps due to their more specific diagnostic. After controlling for the effect of PM₁₀ exposure, increased concentrations of NO₂ were associated with increased admissions in both the dry and rainy seasons, although the risk is more pronounced in the dry season. Neither the individual nor the district level analyses of SEP found that short term exposures to air pollution impact children from different socio-economic backgrounds differently.

DISCUSSION: This is, to the best of our knowledge, the first ever study of the health effects of air pollution in HCMC, and one that focuses on an illness responsible for a substantial burden of disease among young children in developing countries. Increased concentrations of air pollutants are associated with increased hospital admissions for ALRI in young children of HCMC. While these analyses did not suggest differential effects by SEP, there are several reasons why data limitations may hinder the ability to find such relationships.

The Relationship Between Personal and Ambient Exposures in Ho Chi Minh City

HEI Collaborative Working Group on Air Pollution, Poverty, and Public Health in Ho Chi Minh City

In cooperation with an initiative of the Asian Development Bank, an interdisciplinary team of local and international experts is conducting a unique program to assess the health effect of air pollution among the poor in Ho Chi Minh City (HCMC). The project has two complementary components – a hospital-based study and a household-based study (discussed here). In the hospital study, we estimate the effect of short-term exposure to air pollution on hospital admissions for acute lower respiratory infections in young children (<5 years) in HCMC, and compare the magnitude of the effect of air pollution on poor children vs. other children. The poor may experience higher actual exposures to air pollution than the non-poor, but this would not be reflected by the ambient monitors used to assess exposure in the hospital study. Therefore, there is a need to assess the extent to which localized sources may contribute to exposure measurement error arising from the use of ambient monitoring site data for estimating the health impacts, particularly for different sub-groups. The objective of the hospital study is to assess determinants of personal exposure for the poor and non-poor, and to explore whether the use of ambient monitors as a surrogate for personal exposures results in differential exposure misclassification by socio-economic status (SES).

A household survey including detailed questions on household assets and expenditure, as well as the prevalence of chronic respiratory symptoms, was administered to 1000 households in Binh Thanh District and District 2. Based on the results of this survey, 64 households (32 from each district) from the lowest and fourth highest expenditure quintiles were selected. In order to enhance linkage with the hospital study component, primary caregivers of young children (under five years of age) in these households were selected to participate in the study.

Between July 2007 and March 2008, 9 repeated measurements of daily average personal exposures to $PM_{2.5}$, PM_{10} , NO, and NO_2 were made for each participant. Detailed information on exposure to potential sources of pollution, including traffic exposure, incense, cottage industries, and tobacco smoke, as well as time activity patterns, was collected during each measurement period. Personal monitoring equipment was collocated at ambient monitoring stations closest to the two districts to enable a comparison of personal exposures and ambient concentrations.

Hypotheses to be addressed include whether the poor are more exposed to air pollution, and whether the exposures of the poor are more closely linked to ambient air pollution. Preliminary results based on a subset of the repeated measurements will be presented. Personal exposures to $PM_{2.5}$ do not vary much by district or SES, although the poor experience slightly higher exposures than the non-poor in District 2. Daily average concentrations of $PM_{2.5}$ and PM_{10} appear to be much better correlated with personal exposures of the non-poor than the poor.

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

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The Congestion Charging Scheme (CCS) is a traffic management scheme introduced to reduce the numbers of vehicles entering central London during the working week. Our study developed methods to evaluate the possible effects of this scheme on air quality, by comparing pre and post CCS periods within and outside the congestion charging zone (CCZ).

The comparative emissions scenarios for the CCZ and surrounding areas suggested that the introduction of the CCS would lead to a decrease in mean NO_x levels of 1.7 ppb and PM₁₀ concentrations by an average of 0.8 µg/m³ inside the zone. In contrast, a 0.1 ppb increase in NO₂ was predicted within the zone. This was partly explained by an increase in primary NO₂ emissions arising from the introduction of particle traps on diesel buses as part of associated improvements in public transport.

To assess the actual impact of the CCS on air quality, geometric means, 2 years before and 2 years after the introduction of the scheme were compared. Temporal changes within the zone were compared to changes, over the same period, at similarly sited monitors well away from the zone boundary. The analysis focused on (a) the hours (and days) on which the scheme was in operation and (b) vehicle derived pollutants (NO, NO₂, NO_x, PM₁₀ and CO). Based upon the limited data available from within the CCZ, analysis suggested that the implementation of the CCS did not lead to a change in roadside measurements of oxides of nitrogen (NO_x, NO and NO₂) during the hours of operation of the CCS. There was also no evidence to suggest that background concentrations of NO_x measured during the scheme's operation had changed as a result of its implementation. Evidence was however obtained which suggested that background concentrations of NO and NO₂ increased slightly within the zone. Although again based upon limited data, background concentrations of PM₁₀ and CO fell within the zone compared to the control area.

A further aim of the study was to examine particulate oxidative activity. Whilst London PM₁₀ was found to have remarkably high oxidative activity, with evidence that this was enhanced at roadside locations, this did not change at the single within zone site (background site) examined following the introduction of the CCS. In contrast, compositional changes in PM₁₀ were noted at the within zone site, with significant reductions in Cu and Zn, perhaps reflecting decreased brake and tyre wear usage, compared with increases in these metals at all sites outside the zone in the 3 years following the scheme's introduction. This pattern is consistent with increased vehicle usage throughout London, but reduction in vehicle numbers entering the zone.

Overall the study was restricted by not having a sufficient number of monitoring sites within the CCZ. In particular, only one of the monitoring sites situated within the CCZ was at a roadside location. Results derived from this one site was an inadequate basis on which to evaluate a complex urban traffic management scheme. The CCS was not designed to improve air quality, and it appears to have made no or only a small improvement. The extension of the scheme into west London in 2007 may lead to a measurable effect due to the greater area covered (2.6% versus 1.4% greater London).

The London Low Emission Zone Baseline Study

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On 4 February 2008, the world's largest Low Emission Zone (LEZ) was introduced across Greater London. By restricting the entry of the oldest and most polluting vehicles, the LEZ presents a unique opportunity to estimate the impact of reduced vehicle emissions on air quality and health. Prior to undertaking such an investigation, we performed a pilot study to accumulate robust, baseline data.

To assess pollutant concentrations before the implementation of the LEZ, we assembled a comprehensive monitoring network close to trunk routes and major intersections. This was achieved by utilising modelling output difference plots to identify those areas predicted to experience the greatest change in NO₂ (at least 3 µg/m³) and PM₁₀ (0.75 µg/m³). Seven key monitoring sites were identified, and these have been used to produce a robust baseline LEZ air quality dataset and detailed vehicle profiling dataset.

We hypothesised that the LEZ will decrease the oxidative potential of ambient PM₁₀ and PM_{2.5}, in association with altered traffic densities and vehicle mix. To address this, we established the first dataset that describes in detail, the oxidative potential and metal content of a major city's PM₁₀ and PM_{2.5} airshed. We found evidence that particles from roadside locations are more active than those from background sites, which appears to reflect elevated concentrations of Cu, Ba, Mo and BPS-mobilisable Fe, largely associated with the coarse PM fraction. We speculate that the latter may reflect emissions from brakes, or other mechanical wear processes.

The final component of this baseline study established the feasibility, in ethical and operational terms, of using the UK's electronic primary care records to evaluate, through consultations and prescriptions, the effect of the LEZ on health outcomes. This was achieved by creating an analytical dataset from a group of pilot general practices (13 distributed across London with 100,000 patients; 29 situated in the Inner London Borough of Lambeth with 200,000 patients) for which ethics approval was obtained to link, via postcodes (ultimately removed to preserve anonymity), modelled pollutant concentrations to individual primary care records.

The work undertaken in this pilot study provides a solid foundation for LEZ evaluation studies. Our extensive impacts monitoring network, measuring a comprehensive set of pollutants (including a range of particle metrics) provides a unique opportunity to assess both the impact on air quality overall and, specifically, will help to further our understanding of the link between PM composition and toxicity. Finally, based on the population distribution of predicted changes in pollution exposure gained from this research, we believe that the use of primary care databases forms a sound basis, and has sufficient power to evaluate the health impact of the LEZ.

PM Surface–Lung Interactions: Cell Responses to Modified Particle Surfaces

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This project tested the hypothesis that opsonisation of depositing particulate matter (PM) by the lung lining layer alters the behaviour of particles *in vitro* and the cellular responses of A549 lung cells. Different experimental approaches aimed to demonstrate particle-lung lining interactions and measure cellular responses to modified PM surfaces. The study objectives were to (1) determine PM_{2.5}–lung lining liquid interactions, (2) determine the clinical significance of PM-lung opsonin interactions, and (3) offer a plausible explanation for underlying susceptibility of subpopulations exposed to PM.

To understand how PM_{2.5} are modified by lung lining liquid, Factor Analysis (FA) of TOF-SIMS data from 35 non-treated, human lavage (BAL) treated and control urban PM_{2.5} surface information was used to separate samples by treatment type, using only surface chemistry (mass fragment) measurement data. Aggregation of well-characterised particles was measured in isolated lung lining layer components using light scattering techniques to observe size distribution changes and optical microscopy to confirm the shape and density of aggregates. Zeta potential was a relative and quantitative measure of surface charge change in different solutions. A549 lung cell IL-6, IL-8 and TNF- α responses were measured to test the clinical significance of the changes in particle characteristics. Low concentrations were used.

Using data from previous studies, mass fragment markers of surfactant lipid and amino acids were identified on PM_{2.5} surfaces, but not on control or saline treated surfaces. This demonstrated adsorption of lung lining liquid components to PM_{2.5}, even at dilute concentrations (Kendall, 2007). Aggregation and surface charge measurements of different sized and functionalized particles suspended in isolated lung lining layer component dilutions showed that particle size, surface charge and agglomeration behavior changed significantly in the presence of different lung proteins and surfactant lipid. Original particle surface influenced subsequent behavior and surface charge, but the coating proteins/lipid masked the original surfaces and pushed the zeta-potential towards zero. Components of lung lining fluid were therefore shown to modify particle surfaces in a uniform way, largely irrespective of PM surface type, and promote aggregation. In cell models, by varying particle surface chemistry it was possible to promote and suppress cell responses. Particle size was also an important determinant of IL-6 and IL-8 responses; no TNF- α responses were detected at these low concentrations.

In this study, opsonisation of fine particles was shown to occur at much lower concentrations of lung lining layer components than found physiologically, and to affect cell response, even at low particle concentrations. Since the coating of deposited PM by host proteins may modulate their biological activity, as they do for infectious particles, studies of such interaction provide new information as to how inhaled pollutants may induce pulmonary and cardiovascular toxicity.

Update on Phase 1 of the Advanced Collaborative Emissions Study (ACES-1)

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Background. In 2007, on-highway heavy-duty diesel engines (HDDE) were required to meet a particulate matter (PM) emission standard of 0.01 g/hp-hr, a 90 percent reduction from the previous level established in 1994. The nitrogen oxides (NO_x) level in 2007 was limited to 1.2 g/hp-hr, a 50 percent reduction from the 2004 NO_x standard. In 2007, HDDE were equipped with filtered crankcase ventilation, exhaust gas recirculation (EGR) or clean gas induction (CGI), and high efficiency catalyzed diesel particulate filters (DPF) with some means of active regeneration.

With all these changes to on-highway diesel engines, it was important to perform a detailed exhaust emission characterization as called for in ACES-1 in order:

- to quantify the significant reduction in both regulated and unregulated emissions that can be achieved by advanced diesel engines,
- to highlight the emission of new or remaining compounds that may be considered a potential health concern, and
- to help conduct a meaningful health effects study as planned under Phase 3 of the ACES using the most current information and in consideration of issues identified from ACES-1.

ACES-1 focused on the measurement and characterization of regulated emissions and as many as 700 compounds of unregulated emission species present in the exhaust of four modern (model year 2007) HDDE. The engines were supplied by four major engine manufacturers that include Caterpillar, Cummins, Detroit Diesel, and Volvo, and the 2007 engine lube oil was provided by Lubrizol. Engine testing under ACES-1 was recently completed and data analysis is currently underway. At the conclusion of the data analysis for all four engines, one engine will be selected, based on a defined statistical criterion, for a detailed health study at the Lovelace Respiratory Research Institute, under Phase 3 of the ACES.

ACES-1 is sponsored by the Coordinating Research Council and the Health Effects Institute. Funding for the ACES has been provided by the U.S. Department of Energy (DOE), the U.S. Environmental Protection Agency (EPA), the California Air Resources Board (CARB), the American Petroleum Institute (API), the Engine Manufacturers Association (EMA), and Manufacturers of Emissions Control Equipment (MECA).

ACES-1 was performed by Southwest Research Institute in collaboration with Desert Research Institute.

Methods. The federal test procedure (FTP) transient cycle, two CARB cycles, and one 16-hour transient cycle, developed to be used for the health study, were used for emissions characterization from all four engines. Regulated emissions of NO_x, carbon monoxide (CO), non-methane hydrocarbons (NMHC), and PM were measured in accordance with EPA code of federal regulations Part 1065. Unregulated emission species such as particle size and number, organic carbon, elemental carbon, elements, nitrogen dioxide (NO₂), nitrous oxide (N₂O), volatile and semivolatile hydrocarbons, carbonyls, nitrosamines, polycyclic aromatic hydrocarbons (PAH), nitro-PAH, and dioxins/furans were all measured using best established measurement and analytical techniques.

Summary. ACES-1 will provide a unique and very essential database on regulated and unregulated emissions from modern on-highway HDDE. The data acquired from each of the engines in ACES-1 will be used to select an engine suitable for animal testing in Phase 3 of the ACES. The final report on ACES-1 is scheduled to be released in February, 2009.

Extended Follow-Up and Spatial Analysis of the American Cancer Society Study Linking Particulate Air Pollution and Mortality

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This report presents results of an extended follow-up and spatial analysis of the American Cancer Society (ACS) Cancer Prevention Study II (CPS-II) cohort to further examine associations between long-term exposure to particulate air pollution and mortality in large US cities. The current study sought to clarify outstanding scientific issues on the chronic effects of air pollution on mortality. Specifically, we examined (i) the confounding and modifying effect of community and neighbourhood level ecological covariates on the air pollution–mortality association at various scales; (ii) how spatial autocorrelation and multiple levels can be taken into account within the random effects Cox model; (iii) the impact of refinement of air pollution exposure to the within-city or intraurban scale using land-use regression on the size and significance of health effects in Los Angeles and New York; and (iv) an evaluation of critical exposure time windows most relevant for the air pollution-mortality association. The extended 18-year follow up included vital status data for the CPS-II cohort with multiple cause-of-death codes (through December 31, 2000) and more recent exposure data from air pollution monitoring sites for the metropolitan areas.

The influence of covariates obtained from the 1980 US Census on the air pollution-mortality association were examined at the zip code level (ZCA), the metropolitan statistical area level (MSA) and by the value of the difference obtained between the mean ZCA value and the MSA value (DIFF). In contrast to previous analyses, risk estimates increased with the inclusion of ecologic covariates at all scales. The inclusion of ecologic covariates at both the MSA and DIFF scale simultaneously increased the hazard ratio for mortality from ischemic heart disease (IHD) associated with particles less than 2.5 μm in median aerodynamic diameter ($\text{PM}_{2.5}$) (2000 levels) and SO_4 (1990 levels) by 7.5 and 12.8%, respectively.

The results of the Los Angeles spatial analysis found health effects nearly three times greater than earlier analyses using between-community exposure contrasts, suggesting that chronic health effects associated with intraurban gradients in exposure to $\text{PM}_{2.5}$ may be even larger than previously reported associations across metropolitan areas. However, unlike the LA results, mortality for all-cause, cardiopulmonary, and lung cancer deaths was not elevated in the New York City spatial analysis. Large and significant effects were seen for IHD, providing evidence of a specific association with a cause of death that has high biologic plausibility. These results were robust to control for 44 individual variables and for clustering in the random effects. Effects were mildly reduced by inclusion of zip code unemployment.

In comparison to more distal exposures, models using $\text{PM}_{2.5}$ and SO_2 exposures from the most recent five years provided a better fit to available data on mortality from all causes, lung cancer, and cardiopulmonary disease, as evidenced by lower Akaike's Information Criteria (AIC) values.

The epidemiological results reported here are consistent with those from other population-based studies, which collectively strongly support the hypothesis that long-term exposure to $\text{PM}_{2.5}$ increases mortality in the general population.

Association of Air Pollution and Mortality in Ludhiana City of India: Preliminary Results of a Time-Series Study

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Background: Most of the studies on air pollution and health have been conducted in the industrialized countries of the North. Climatic conditions, characteristics of the population, and the composition of air pollutants may have important bearing on the health effects of air pollution. In the sub-tropical climate of India, a time series study was carried out in Ludhiana city to estimate the effect of air quality on mortality.

Methods: Located in Northern India, Ludhiana city is the largest city of Punjab state with population of 1.5 million and an area of 135 square kilometer. The data on air quality, meteorology and mortality was collected from Ludhiana for three years, i.e., 2002, 2003, 2004. Punjab Pollution Control Board monitored air quality (RSPM, NO_x and SO₂) at 4 stations in Ludhiana by high volume air sampler using gravimetric method for RSPM and chemical method for NO_x and SO₂. However, two of the stations functioned on three days of the week and the other two functioned on the remaining three week days. Temperature, relative humidity and visibility data was recorded by meteorology department. Daily mortality data was recorded by Municipal Corporation. City daily average of RSPM was derived by averaging the daily average of each of the station. Association of all cause mortality with RSPM was studied using generalized additive model with penalized and natural spline smoothers in R having smoothers for temperature and relative humidity in the model.

Results: The level of RSPM ranged from 50 to 754 µg/m³, SO₂ from 6 to 36 µg/m³ and NO_x from 15 to 89 µg/m³. Mean (SD) temperature was 25.6 (7.9) degree Celsius and relative humidity was 58.1(19.3) percent. Overall 27840 deaths were registered; with an average of 25.4 deaths per day (standard deviation of 5.8). Large seasonal variations were observed in temperature and relative humidity. In preliminary analysis, at 0 lag day, beta coefficient for relation of RSPM and mortality was found to be 5.6×10^{-5} ($p = 0.5$).

Conclusion: Air quality was found to be associated with mortality in Ludhiana city, however, the association was not statistically significant. Age and sex specific analysis of natural deaths will be carried out.

Increased Sensitivity of Elderly Mice to Inhaled Diesel Exhaust

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Background: Epidemiologic studies have demonstrated strong associations between ambient fine particulate matter (PM) and cardiovascular morbidity and mortality with the elderly being particularly susceptible. Diesel exhaust (DE) particles are a major component of urban PM. The mechanisms by which DE particles induce injury in the cardiovascular system remain unclear, and this was investigated.

Methods: A Yanmar 5500 cc one-cylinder, two cycle, diesel-powered electrical generator was used as a source of DE. The engine was run on low-sulfur diesel fuel under 100% of rated load. The emissions were aged in the delivery system and then diluted with HEPA-filtered air in the exposure chamber (17-liter whole body plexiglass enclosure, 16" x 8" x 8"). DE concentrations in the chamber were controlled by adjusting the fraction of total DE directed towards the chamber and by the amount of the dilution air in the chamber. CB6F1 male mice (2 mos and 18 mos) were exposed to ultra pure air or DE containing 300 $\mu\text{g}/\text{m}^3$ or 1000 $\mu\text{g}/\text{m}^3$ of particles for 3 hr (single) or for 3 hr/day for three consecutive days (repeat). Bronchoalveolar lavage fluid (BAL), serum and lung tissue were collected 0 hr and 24 hr later, and analyzed for markers of injury and oxidative stress.

Results: Exposure of mice to DE resulted in increased levels of protein and lactate dehydrogenase in BAL fluid, indicating damage to the lower lung. Older mice were more sensitive to the cytotoxic effects of DE than younger animals. Greater numbers of macrophages were also detected in BAL fluid of older animals. No differences were noted between the single and repeat DE exposure protocols. While a single low dose (300 $\mu\text{g}/\text{m}^3$) of DE particles had no significant effects on lung histology in either younger or older animals, repeated exposure of older animals to DE resulted in patchy thickening of alveolar septa, cytomegaly in alveolar septal walls and increased numbers of macrophages in alveolar spaces, which was evident immediately after exposure. By 24 hr post exposure, older mice also developed bronchial epithelial necrosis, focal thickening of alveolar septal walls and increased numbers of neutrophils and erythrocytes were evident. Structural alterations were mild in younger mice when compared to older animals. With both single and repeated high dose (1000 $\mu\text{g}/\text{m}^3$) DE exposure, significantly more inflammatory changes, including increases in neutrophils in alveolar spaces and capillaries, and focal inflammatory infiltrates consisting predominantly of plasma cells and macrophages, were noted in older when compared to younger animals. These changes were evident immediately (for repeat DE) or after 24 hr (for single DE) exposure. We also noted that expression of the antioxidant superoxide dismutase (SOD) decreased in the lungs of younger animals after repeated exposure to DE; in contrast expression of SOD increased in older animals.

Conclusions: These data demonstrate that older mice are more sensitive to lung injury induced by inhaled DE. Furthermore, differences in induction of antioxidant enzymes such as SOD, may be important in the pathogenic response to DE in older mice.

Assessing Indoor and Outdoor Residential PM_{2.5} Source Contributions Using GIS and Non-Negative Matrix Factorization

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Background Numerous epidemiological studies have evaluated the relationship between fine particulate matter (PM_{2.5}) and respiratory and cardiovascular health outcomes. Within urban environments, there has also been growing interest in the effects of proximity to traffic, although with limited identification of causative agents. Disentangling the effects of various particle constituents is complicated by the numerous indoor and outdoor sources contributing to personal exposures, as well as the difficulty in determining exposures to these sources in the context of a large epidemiological study, where exposures cannot be measured as extensively. In this study, we develop regression models to predict latent variables for indoor and outdoor pollution sources as a function of GIS and questionnaire data available for a larger cohort.

Methods As part of a prospective birth cohort study in urban Boston, we collected indoor and outdoor 3-4 day samples of nitrogen dioxide (NO₂) and PM_{2.5} in 43 homes in summer and winter from 2003 – 2005. Reflectance analysis, X-ray fluorescence spectroscopy (XRF), and high-resolution inductively-coupled plasma mass spectrometry (ICP-MS) were performed on particle filters to determine elemental carbon (EC), trace element, and water-soluble metal concentrations, respectively. To disentangle source contributions, we fit factor analysis models with loading matrices constrained to positive entries, as in Non-Negative Matrix Factorization (NNMF). To help determine the appropriate number of factors, we developed exploratory interpretability plots that determined the “sharpness” of hypothesized source categories for varying number of factors. Regression models predicting outdoor latent variables utilized GIS-based traffic and outdoor source terms, central site monitoring data, meteorology, and other relevant covariates. Models based on indoor measurements additionally considered indoor sources from questionnaires (e.g., smoking, cooking) and terms representing ventilation.

Results A five-factor model was chosen for outdoor concentrations, with the structures of the factors indicating contributions from long-range transport, brake wear and other traffic, diesel combustion, fuel oil combustion, and road dust. Regression models confirmed our initial factor interpretations, as the long-range transport factor was strongly predicted by central site PM_{2.5}, the traffic-related terms by traffic and road density covariates, the diesel term by percentage of diesel traffic on the nearest major road, and the fuel oil term by population and road density. Indoor-outdoor correlation analyses found high correlations for compounds without hypothesized indoor sources (e.g., S, V, P, Se) and non-significant correlations for crustal elements (e.g., Ca, Si), as anticipated. NNMF analyses for indoor concentrations demonstrated more complexity than for outdoor concentrations, given a greater number of sources and the influence of ventilation, but analyses suggest that a subset of outdoor sources (e.g., fuel oil, diesel, long-range transport) as well as indoor sources such as resuspended dust and cooking will be separable.

Conclusions Our NNMF and regression results will help in the prediction of key sources of fine particulate matter in indoor and outdoor residential environments, allowing for assignment of exposures within epidemiological studies and assisting in determining the causative sources and factors for health outcomes.

Personal Exposures to and Spatial Variations of Air Toxics in a “Hot Spot” in Camden, New Jersey

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The study characterized personal exposures and ambient concentrations of air toxics in a “hot spot” area - The Village of Waterfront South (WFS), and an urban reference site, Copewood/Davis Streets area (CDS), in Camden, NJ. Personal exposure and residential ambient air measurements, along with statistical analyses and exposure modeling, examined the impact of local industrial and mobile sources, particularly diesel exhausts.

Personal (54 non-smoking subjects from WFS and 53 from CDS) and ambient air samples from a fixed monitoring site in each neighborhood were collected for 24 hours and measured 11 VOCs, 4 aldehydes, 16 PAHs, and PM_{2.5}. Three “Spatial Saturation Sampling” campaigns were conducted to monitor VOC and aldehyde concentrations for 24-48 hours at 22 and 16 grid-based sampling sites in WFS and in CDS, respectively.

Results showed that ambient PM_{2.5} (31.3±12.5 µg/m³), toluene (4.24±5.23 µg/m³), and benzo(a)pyrene (0.36±0.45 ng/m³) were significantly higher ($p < 0.05$) in WFS than in CDS. High concentrations of 60 µg/m³ for toluene and 159 µg/m³ for MTBE were found in areas close to local stationary sources in WFS during the spatial variation study. Great spatial variability BTEX and MTBE was observed in WFS, indicating impact of local sources. Similar mean concentrations of benzene and MTBE and a good correlation ($R > 0.6$) between these two compounds in WFS and CDS suggested automobiles as main sources. Formaldehyde and acetaldehyde were high in both WFS and CDS (e.g. mean concentrations of formaldehyde were > 20 µg/m³ in both locations), suggesting a large impact from local diesel truck traffic for formaldehyde and acetaldehyde pollution.

Personal concentrations of toluene (25.4±13.5 µg/m³) and acrolein (1.78±3.7 µg/m³) were higher in WFS than in CDS (13.1±15.3 µg/m³ for toluene and 1.27±2.36 µg/m³ for acrolein). The higher personal levels of some compounds (e.g. benzene) in CDS partially resulted from ETS or occupational exposure.

The simulated ambient concentrations of benzene and toluene using dispersion models were generally consistent with the ambient measurements within a factor of 2, but underestimated at the high-end percentiles. The modeled ambient concentrations of formaldehyde only accounted for 4-20 % of the ambient measurements, which was partially due to the underestimation of emission from local traffic. The source attributions showed that mobile sources are the major contributors to ambient levels of benzene and formaldehyde, while both mobile and stationary sources contributed equally to toluene. Personal exposure modeling using the Individual Based Exposure Modeling application of the MENTOR system showed that the modeled benzene and formaldehyde personal concentrations based on the ambient measurements were comparable to the personal measurements, suggesting strong impacts from local ambient sources. However, the modeled toluene personal concentrations were consistently lower than the personal measurements, suggesting the strong influences of indoor sources.

In conclusion, this study demonstrated that WFS is a “hot spot” for *specific* air toxics. The “Spatial Saturation Sampling” was essential for increasing understanding of the spatial distribution of air toxics and identifying the sources of concerns. The sampling and modeling approaches implemented provide valuable tools for future in “hot spot” health studies and control strategies.

Characteristics of PM Associated with Health Effects

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Background: Previous studies have reported significant associations between PM_{2.5} and daily and annual mortality, morbidity, and lost time and lung function, but little is known about the roles of specific PM_{2.5} components and sources.

Objective: Identify and quantify the influence of specific ambient air components and sources of PM_{2.5} with associated health effects.

Experimental Design: We developed an integrated approach involving four subprojects, all considering PM speciation and exposures to ambient air particulate matter (PM) from a variety of US airsheds, including: 1) subchronic inhalation exposures (6h/d, 5d/wk, 6 months) of a murine model of atherosclerosis to concentrated ambient PM_{2.5} (CAPs) in NYC, Tuxedo NY, Seattle WA, Ann Arbor MI, and Anaheim CA; 2) *in vitro* & aspiration exposures of mice to PM collected in the same locations in 3 size ranges; PM_{2.5-10}, PM_{2.5}, and PM_{<0.2}; 3) time-series regressions of daily hospital admissions and mortality by-cause on PM_{2.5} and its components in multiple U.S. MSAs; and 4) statistical analyses of annual mortality in the ACS cohort with PM_{2.5} components. Results of these laboratory and epidemiological studies will be examined to determine whether any specific components and/or sources are more associated with specific short-term or long-term health effects.

Tasks Completed: During the first year of this 4-yr study, we completed: 1) simultaneous 6-month CAPs inhalation exposures of mice in NYC and Tuxedo NY; 2) collection of size-selective high volume winter-time air samples in the 5 US airsheds where the 6-month inhalation studies have been or will be performed; 3) assembled, quality assured, and characterized 2000-2006 speciation data in terms of uncertainty, signal-to-noise ratio, monitor-to-monitor correlation, and temporal patterns in 21 candidate US MSAs, and have retrieved census, land use, traffic count and emission data for land-use regressions; 4) conducted nationwide source apportionment analyses of the daily speciation data (>60,000 samples); and 5) explored the use of 3-dimensional factor analysis of speciation data.

Findings: 1) During the simultaneous 6-month inhalation studies in NYC and Tuxedo NY, the CAPs mass concentrations were similar in both locations, while the black carbon concentrations were 3 times greater in NYC. Comparisons of plaque in the aortas of the sham air exposed mice to the CAPs exposed mice in terms of % coverage by ultrasonic bioimaging after 3-months of exposure indicated 13 vs. 27% for the Tuxedo mice (p<0.01), and 17 vs. 20% (p=0.45) for the NYC mice. Analyses of speciation filters and other endpoints are in progress. 2) Analyses of *in vitro* responses to the winter-time samples will be performed simultaneously with those of the summer-time samples to be collected in the 2nd year; 3) the nationwide source apportionment analysis has identified eight dominant PM_{2.5} components (and key tracers): Soil (Si, Ca), Coal (Se, As), Oil (V, Ni), Traffic (EC, OC), Steel (Fe, Mn), woodburning (K), Metals/Incineration (Pb, Zn), and Salt (Na, Cl); 4) preparations for time-series analyses are in progress; and 5) cohort mortality analyses will begin once the ACS database follow-up is extended to overlap the Speciation Network sampling period.

Status of the Advanced Collaborative Emissions Study, Phase 3: Chronic Inhalation Bioassay

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Purpose. The core of the ACES program is Phase 3, the conduct of an animal study of the health hazards of emissions from 2007 technology large on-road engines. The study was contracted to a multi-institutional research team coordinated by the Lovelace Respiratory Research Institute (LRRI). Multiple health outcomes will be evaluated, and the study design meets criteria for a chronic inhalation cancer bioassay. The study will test the sponsor's hypothesis that "emissions ... will have very low pollutant levels and will not cause an increase in tumor formation or substantial toxic effects in rats and mice at the highest concentration of exhaust that can be used ... compared to animals exposed to clean air, although some biological effects may occur".

Approach. An engine selected on the basis of Phase 1 emissions comparisons will be installed at LRRI. The engine will be operated on a variable duty cycle and burning fuel as specified in Phase 1, primary dilution of emissions will occur at constant diluting flow, and portions will be further diluted to exposure concentrations which are yet to be selected. Groups of 288 Wistar rats will be exposed by inhalation in whole-body chambers 16 hours/day, 5 days/week for up to 24 months to each of three concentrations of diluted emissions and to clean (diluting) air as controls. Each of the four exposure groups will include 166 rats for the cancer bioassay and 122 rats to be evaluated after 1, 3, 12, or 24 months of exposure for non-cancer effects. Groups of 120 C57BL/6 mice will be similarly exposed, but all will be evaluated for non-cancer effects after 1 or 3 months of exposure. Tumors will be identified histologically. Non-cancer assays will include pulmonary function (rats only), bronchoalveolar lavage, lung cell proliferation, serum chemistry, necropsy and histopathology. LRRI will also facilitate additional evaluations yet to be selected from among those proposed in response to a companion RFA.

Status. The study team has been assembled, background information has been reviewed, the location and capacity of the engine facility have been selected from among multiple options, and key decisions have been made regarding selection of animal strain and the fundamental study protocol. Current effort is directed toward renovating the pre-existing LRRI engine facility to accommodate larger engines than have been used in past LRRI studies. Pre-existing dynamometers and engine cooling and control systems have been removed and are being installed in a new location to conduct exposures for the HEI NPACT program. Reconstruction of the older facility is underway to accommodate larger dynamometers, different fuel and control systems, greater cooling and diluting air capacity, and a new dilution tunnel. Exposures of animals are estimated to begin in late 2008.

***Houston Exposure to Air Toxics Study**

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Background. In 2005, the study authors, state and federal agencies and local research and stakeholder groups secured funds for and initiated the Houston Exposure to Air Toxics Study (HEATS). While significant ambient monitoring data for hazardous air pollutants (HAPs) exists for Houston, Texas, there is a lack of personal exposure data for the region. The study objective is to determine if personal exposures to a select group of HAPs experienced by residents of the Ship Channel area of Houston, which has a high density of point sources of HAPs, are higher than personal exposures of residents of a demographically similar area of Houston (Aldine), which has few such sources.

Methods. Two study areas are included: the Houston Ship Channel and Aldine. The census tracts comprise a similar size area, with similar sociodemographic characteristics. A probability-based representative sample of 100 nonsmoking adults 21 and older in each area (and one child in half the households) is being recruited. Data is collected on two separate occasions of four household visits each:

- Parallel 24-hour average concentrations of indoor, outdoor, personal and fixed site air toxics
- Participants' indoor-outdoor activities while monitored
- Residential air exchange rates
- Neighborhood and residence characteristics (including indoor emissions sources)
- Participant sociodemographic characteristics
- Health symptoms and risk perception

Personal exposure is measured using a tube-type passive sampler employing Carbopack X which was developed by EPA and used in the Detroit Exposure and Aerosol Research Study. Health symptom and risk perception data is being collected. A multi-faceted education, outreach and communications plan is being implemented.

Results. A pilot study was conducted in September 2007. The main study began in October 2007, and will continue through September 2008. Recruitment of study participants in the targeted neighborhoods is proving challenging due to a variety of factors. All materials and study elements are conducted in English and Spanish. The communication plan implementation focus has been on overcoming participant resistance to participation through local community leader meetings, distribution of study literature broadly in the community, press releases, an increase in the amount of incentive payment to participants, improved identification of study recruiters via a simple uniform, and targeted public service announcements to study neighborhoods.

Conclusions. The field study is ongoing. Communication, education, and outreach efforts will be increased and alternative methods are being explored to enhance recruitment of participants. The final report and results are expected in February 2009. The HEATS study is expected to provide a wealth of new data on personal exposure to HAPs in two Houston neighborhoods. In addition, the study will contribute significantly to the existing literature on study design, methods development for the target HAPs, recruitment of participants in challenging environments, and coalition building of multiple sponsors to perform significant new research.

* Study not funded by HEI.

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

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The goal of this project is to conduct an accountability analysis of Phase 2 of the Acid Rain Trading Program by connecting changes in ambient $PM_{2.5}$ concentrations measured at selected air quality monitors in the eastern US with SO_2 and changes in NO_x emissions from electric utility generators subject to the SO_2 emission caps. In this second year of the project we completed data assembly and assessed the implications of the missing daily ambient data for the precision of the monthly estimates to be used in the statistical analysis. Specifically, we developed a relationship between the number of available observations, the maximum gap between any successive observations, and the mean error and bias of estimated monthly means. The basic finding is that even with as few as 6 daily observations that are not too widely spaced, it is possible to estimate monthly means with reasonable precision. Based on very recent work, we report some initial modeling results using a Bayesian belief net which suggests a statistical link between sources and receptors.

Impact of Community Wood Stove Changeout on Ambient and Indoor Air: Interim Results

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Background: Like many mountain valley communities which experience cold temperature inversions, Libby, MT suffers elevated concentrations of PM_{2.5} during the winter months due to emissions of wood smoke from domestic heating. In an effort to meet the National Ambient Air Quality Standards (both daily and annual), over 1000 wood stoves were replaced, reconditioned, or decommissioned starting in 2005 and continuing through 2007,

Objectives: The purpose of this study is to evaluate the changes in community exposure to wood smoke and the impact on children's health before, during, and after a community intervention project that will reduce PM_{2.5} emissions from domestic wood stove usage. In particular, exposures, reporting of symptoms, and school absences will be evaluated among school-aged children in Libby, MT over a period of three years. Presented here are interim results of changes in the concentrations of PM_{2.5} and chemical markers of wood smoke at a central site sampling location, and within several homes.

Methods: At the Montana Department of Environmental Quality monitoring site for Libby, ambient levels of PM_{2.5} are measured every 3 days following EPA's fixed monitoring schedule. In addition we collected PM_{2.5} quartz filters to analyze for specific chemical markers of woodsmoke, including levoglucosan. Inside homes, two samplers (one TSI DustTrak that continuously measures PM_{2.5} mass, and one Leland pump/Personal Environmental Monitor (PEM) sampler fitted with a quartz filter for OC/EC and chemical markers of wood smoke analyses) were deployed for 24-hour pre- and post-wood stove changeout sampling events.

Results: At the compliance monitoring site, winter average concentrations of both PM_{2.5} and levoglucosan were lower during the interim years compared to baseline, or pre-changeout program, years. In selected homes undergoing wood stove changeout, both PM_{2.5} and levoglucosan concentrations were lower following the introduction of a new wood stove. Other wood smoke markers such as resin acids and methoxyphenols did not consistently track with the reduction in indoor PM_{2.5}.

Conclusion: These interim results suggest that the community-wide wood stove changeout program was effective in reducing PM_{2.5} in both ambient and indoor environments. Forthcoming data will help to determine if these changes are sustained and if such changes have a corresponding health impact on susceptible populations.

Microvascular Inflammatory Mechanisms Activated After Inhalation of Ultrafine Particulate Matter

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Overview: We have shown that pulmonary exposure to fine particulate matter (PM) impairs endothelium dependent dilation in systemic arterioles, and this impairment is augmented after ultrafine PM exposure. The purpose of this study was three-fold: 1) determine if PM size affects the severity of post-exposure microvascular oxidative stress, 2) characterize alterations in microvascular nitric oxide (NO) production after PM exposure, and 3) determine if any such alterations in microvascular oxidative stress are associated with NO production and/or arteriolar dysfunction.

Methods: Rats were exposed to fine or ultrafine TiO₂ via inhalation (mean particle diameters of ~1 μm, and ~123 nm, respectively) at calculated depositions of 0.15, 0.1, 0.06, 0.03, 0.015, and 0.007 mg/rat (actual depositions measured via inductively-coupled plasma-atomic emission spectroscopy). The spinotrapezius muscle was prepared for in vivo microscopy 24 hrs after pulmonary exposures. Intraluminal infusion of the Ca²⁺ ionophore A23187 was used to evaluate endothelium dependent arteriolar dilation (a process heavily dependent on NO). Microvascular oxidative stress was measured via ethidium bromide fluorescence. Endogenous microvascular NO production was measured with a Clarke-Type electrochemical NO sensor.

Findings: In control rats, A23187 infusion produced dose-dependent arteriolar dilations. Whereas, in rats exposed to fine TiO₂, A23187 infusion elicited vasodilations that were blunted in proportion to pulmonary particle deposition. In rats exposed to ultrafine TiO₂, A23187 infusion produced arteriolar constrictions or significantly impaired vasodilator responses as compared to the responses observed in control rats or those exposed to an identical pulmonary load of fine particles. Microvascular oxidative stress was significantly increased among both exposure groups. In the fine and ultrafine exposure groups, endogenous microvascular NO production was attenuated after inhalation in a dose-dependent manner. Treatment with antioxidants (2,2,6,6-tetramethylpiperdine-*N*-oxyl + Catalase), the myeloperoxidase (MPO) inhibitor 4-aminobenzoic hydrazide, or the NADPHase inhibitor apocynin partially restored NO production and arteriolar function in both groups.

Summary: Systemic inflammatory mechanisms are activated after PM exposure and such mechanisms disturb normal microvascular function. Because MPO inhibition partially reversed these effects, it appears that hemoprotein deposition is involved in this process. Moreover, these studies are the first to directly quantify deficits in microvascular NO production after PM exposure. These deficits are strongly associated with increased reactive oxygen species production at a crucial level of the circulation. Reversal of such oxidative stress was associated with a partial normalization of both NO production and arteriolar function.

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.

***Multiple Air Toxics Exposure Studies in the South Coast Air Basin of Metropolitan Los Angeles**

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A Multiple Air Toxics Exposure Study (MATES III) was conducted by the South Coast Air Quality Management District (South Coast AQMD) from March, 2004 to April, 2006, to quantify exposure and risk from existing sources of selected air toxic contaminants in greater metropolitan Los Angeles, home to about 16 million residents. This was a follow up study to previous air toxics measurements.

Enhancements from previous studies included monitoring for additional compounds and sampling more often – every 3 days. To supplement use of elemental carbon for estimating diesel particulate levels, several organic compounds within collected PM_{2.5} samples were analyzed. These were used in a mass balance model to apportion diesel and other sources of particulate matter

Ambient monitoring was conducted at 10 fixed sites over the two year period, and complementary shorter term sampling using movable platforms was conducted for several month periods at 5 additional locations. Air toxics emissions inventories were developed which included analysis of all sources of toxic emissions (point, area, and mobile sources in the 6,700-square-mile region). Efforts were also made to spatially allocate emissions for gasoline service stations, dry cleaning operations, and chrome-plating operations. Dispersion modeling was performed using the Comprehensive Air Quality Modeling with Extensions (CAMx) enhanced with a reactive tracer modeling capability (RTRAC). Carcinogenic risks were estimated using CalEPA unit risk factors assuming 70 year exposures and shown spatially for the Basin on a 2 km grid scale.

Based on average concentrations measured at fixed sites, air toxic carcinogenic risk was found to be about 1,200 per million. This is about 14% lower than estimated in the previous MATES II study conducted in 1998 – 99. Mobile sources represented the greatest contributor, with over 80% of all risk attributed to diesel emissions, and about 10% to other toxics associated with mobile sources (including benzene, butadiene, and formaldehyde). Modeling results showed similar levels of risk and also showed strong domination of mobile sources. Highest risk levels were in areas with high diesel activity, including marine ports, near railyards, and near goods transportation corridors.

With few exceptions, monitoring at the temporary sites did not register significantly higher levels of toxic air contaminants, and impacts were dominated by mobile sources.

As there is no technique to directly measure ambient levels of diesel exhaust, the Chemical Mass Balance model approach was used to estimate diesel particulate. Although this technique may have uncertainties, the emissions inventory and modeling (which account for directly emitted diesel particulates) confirmed that diesel particulate was the major contributor to risk.

* Study not funded by HEI.

Assessing the Utility of Satellite Aerosol Optical Depth Data for Retrospective Estimation of Monthly PM_{2.5} Concentrations in the Eastern United States

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Advances in spatial modeling and geographic information system (GIS) technology, combined with the availability of satellite aerosol optical depth (AOD) data as a proxy for particulate matter (PM) estimation, present the opportunity for integrated estimation of PM_{2.5} for use in health analyses of the chronic effects of PM. Our interest focuses on improving prediction of spatial patterns in monthly average PM for use in chronic epidemiological studies. Statistical techniques, in particular Bayesian hierarchical spatio-temporal modeling, provide a natural framework for the integration. Here we investigate the association between AOD and PM using exploratory techniques, showing reasonable correlations for each of several satellite sensors of AOD, including the GOES AOD product, when AOD is available. However, we note high levels of missing AOD retrievals, often because of cloud cover, which cause difficulty in using AOD as a proxy both at the daily and long-term timescales. We then present two Bayesian statistical models to address two key questions. In this initial modeling, we focus on the state of Pennsylvania and surrounding areas for the year 2004.

First, how can we model the possibility of spatially-varying bias in AOD as a proxy for PM? We present a hierarchical Bayesian model that attempts to capture the key features of the available data through multiple likelihood terms, one for each AOD proxy and one for ground-level monitoring data, while accounting for the complicated spatial and temporal misalignment of the data sources. Evidence suggests that the bias does vary spatially, which causes identifiability problems inherent in the structure of the data. We show that predictions of PM in this framework are very sensitive to the flexibility of the model term that represents spatially-varying bias.

Second, does including the AOD proxy materially improve predictions of ground-level PM beyond what can be achieved based on the PM data and various covariates? The raw correlations between AOD and PM indicate potential for the use of AOD as a proxy. However, results from a second model in which AOD is used as a covariate indicate that AOD adds limited additional information for improving predictions of PM relative to a full spatial statistical model that uses a variety of GIS-derived covariates. Consistent with this, in the first model (above), with sufficient flexibility in the spatial bias term, AOD has little impact on the PM predictions. The contrast between the empirical associations and the model results suggest that while AOD acts as a large-scale proxy for PM, it may not reflect fine-scale spatial patterns in PM. The results present concerns about the promise of AOD as a proxy for monthly PM_{2.5} concentrations.

Impact of Improved Air Quality During the 1996 Atlanta Olympic Games on Multiple Cardiovascular and Respiratory Outcomes

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Background: Substantial evidence supports an association between ambient air pollution, particularly particulate matter and ozone, and acute cardiovascular and respiratory morbidity. There is increasing interest in evaluating whether actions taken to reduce air pollution levels will result in reduced morbidity. This study capitalized on a unique opportunity to evaluate the impact of a local, short-term intervention effort to reduce traffic in Atlanta during the 1996 Summer Olympic Games (July 19, 1996 – August 4, 1996).

Methods: Air pollution levels both inside and outside of Atlanta were examined for various time periods. Emergency department (ED) visits for were examined to evaluate changes in usage patterns. ED visits for respiratory and cardiovascular conditions and ventricular arrhythmias were examined in relation to the Olympic time period using Poisson time series analysis adjusting for time trends and meteorologic conditions.

Results: Ozone levels were approximately 30% lower during the Olympic period compared to the four weeks before and after the Olympics. Levels of PM₁₀, nitrogen dioxide, and carbon monoxide were also somewhat lower during this time period, while sulfur dioxide levels increased slightly. We observed reductions of ED visits for asthma and for upper respiratory infections, particularly for pediatric age groups (relative risk [RR] = 0.746, 95% Confidence Interval [CI] = 0.554-1.005 and RR=0.818, 95% CI 0.653-1.024, respectively), during the Olympic time period, as well as an increase in COPD visits during this time period (RR = 1.372, 95% CI = 1.048-1.797). While limited in sample size, we observed fairly large reductions in ventricular arrhythmias in patients with implantable defibrillators during the Olympic time period (RR=0.315, 95% CI = 0.137-0.723).

Conclusions: It is unclear if pollution levels during the Olympic time period were reduced because of the intervention effort or because of prevailing meteorologic conditions. Regardless, air pollution levels were reduced during this 17-day period, and our results provide evidence for reductions in both emergency department visits, particularly for pediatric upper respiratory infections and asthma, and ventricular arrhythmias during this time period.

Development of a Web-Accessible Relational Database for Air Toxics and PM_{2.5} Based on the RIOPA Study

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In the Relationships of Indoor, Outdoor, and Personal Air (RIOPA) study (Weisel et al., HEI Report 130 Part I, NUATRC Report 7, 2005; Turpin et al., HEI Report 130 Part II, NUATRC Report 10, 2007), air concentrations of volatile organic compounds, carbonyl compounds, PM_{2.5}, and PM components were measured in three cities: Elizabeth, NJ; Houston, TX; and Los Angeles, CA. In each city, about 100 homes and their adult and child residents were sampled twice between summer 1999 and spring 2001. The measurements and associated supplementary data constitute a very rich database for future health effects and exposure studies.

To facilitate the use of the RIOPA database, a relational database is being developed in this work, together with a web-based user interface to facilitate data exploration and extraction.

In Phase 1, we have performed a critical review of the available RIOPA dataset. The first element of the review is an accounting of the number of households, households receiving second visits, the number of adult and child subjects, and the households designated for in-vehicle carbonyl, PM mass, PM carbon, and PM element measurements. This accounting sets the expectation for data availability and allows the use of a set of consistent flags to indicate specific reasons for missing data. The second element of the review is a compilation of the methodology used for each type of measurements, and the procedures used to generate the best estimate measurements. This information is an important component of the meta data to be provided alongside measurement data.

In Phase 2, we will design and implement the web-based relational database. An initial database release is slated for Spring 2008, followed by a comment period and a final release in mid 2008.

Information on the HEI Air Quality database (<http://hei.aer.com>) will also be available at the poster session.

***Leveraging Environmental Public Health Tracking for Chronic Disease Prevention**

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Background: The environment we live in can affect our health. However, limited information exists to address basic concerns about our exposure to chemicals and other agents in the environment and the occurrence of health outcomes such as asthma, cancer, birth defects and other chronic conditions. In 2000, the Pew Environmental Health Commission urged that a “Nationwide Environmental Health Tracking Network” be established with the goals of reducing and preventing health problems and increasing our understanding of the relationship between the environment and health. The National Environmental Public Health Tracking (Tracking) Program, with the Tracking Network as its cornerstone, is CDC’s response to calls for providing information to people on how the environment may affect their health.

Methods: Between 2002 and 2006, CDC laid groundwork for a standards-based Tracking Network by building partnership, state and local infrastructure, workforce capacity, analytic tools, and outreach. Data linkage pilot projects served as “proofs of concept”. Workgroups consisting of Tracking grantees, NGOs, and federal partners collaborated with CDC to conceptualize, plan, and implement components of the Tracking Network. In 2006, CDC published a National Network Implementation Plan (NNIP) that clarifies principal functions and components of Tracking Network; discusses the steps needed to implement the components; and identifies the entities responsible for taking the implementation steps.

Results: State and local tracking grantees completed over 50 pilot projects linking health and environmental data. These projects demonstrated the technical feasibility of linking these data for ongoing public health surveillance/tracking; examined methodological and communication issues; and demonstrated the use of Tracking information to drive public health action. Currently 16 states and New York City are funded to implement state-level tracking networks that will be components of the National Network. By the end of 2008, the Tracking Network will provide nationally consistent environmental public health information about lead, carbon monoxide, air, water, asthma, acute myocardial infarction, birth defects, cancer, and reproductive outcomes and a suite of tools and services for its users.

Conclusions: The Tracking Network can provide important information on the health and environmental status of communities; identify areas and populations most at risk from environmental contamination, and inform public health practice and policy. Analysis of data from the Tracking network will provide valuable information on changes or trends in levels of pollutants, population exposure, occurrence of noninfectious health effects, and enable public health practitioners to examine the possible relations among them.

* Study not funded by HEI.

A New Approach to Semiparametric Regression

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The panel that authored the commentary in HEI's Revised Analyses of Selected Time Series Studies was concerned that the substantive interpretation of time series studies of the effect of pollutants on disease was so critically dependent on the validity of point and interval estimates derived from semiparametric regression models. These estimates depend on the degrees of freedom chosen to control potential confounding from temperature, humidity, and time. In the section of our Panel report that I authored, I argued that there was no known scientific way to choose the appropriate number of degrees of freedom because of (1a) the need to allow for many degrees of freedom to prevent the potential for confounding bias under the null hypothesis stands opposed to (1b) the need not to include too many degrees of freedom so as to preserve statistical power to detect pollution effects, (2) the empirical data cannot determine the optimal trade-off between these conflicting needs, and (3) current biological or meteorological knowledge is insufficient to determine the optimal trade-off. As a consequence we remain unsure of the strength of the conclusions that can be validly drawn from these analyses.

The goal of the proposed research to develop such a more scientific approach to semiparametric regression (SR). We are developing a new analytic methodology that we hope may change how one fits high dimensional statistical models, such as SR models, to large data sets. This approach is based on a theory that uses higher order scores and influence functions in place of the first order scores and first order influence functions that are the basis for the current theory of and approach to fitting semiparametric regression models.

In this poster we describe our progress including our first multivariate analyses of the NMMAPS data using our approach and a comparison with other approaches.

Air Pollution and Mortality in Latin America: Results from the ESCALA Project (Multi-City Study of Air Pollution and Health Effects in Latin America)

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Introduction: The ESCALA project (Estudio de Salud y Contaminación del Aire en Latinoamérica) is a HEI funded study that aims to examine the association between exposure to outdoor air pollution and health effects in several Latin American cities, using a common analytic framework in order to obtain comparable and updated information on the effects of air pollution on several cause/age groups. First stage time series analyses (individual cities) have been carried out for different causes and agegroups. We report here preliminary results for Brazilian, Chilean and Mexican cities.

Methods: Generalized Additive Models (GAM) in Poisson regression was used to fit the data. Time trends and seasonality were adjusted by a natural spline with 4 degrees of freedom (d.f.) per year. Indicator variables of the weekdays and holidays were used in order to account for the short term cyclic fluctuation. A natural spline of 1-day lagged mean temperature with 4 d.f. per year and a natural spline of 1-day lagged humidity with 2 d.f. per year were used to adjust for meteorological factors. Single lag and distributed lag models were fitted to particulate matter (PM₁₀) and ozone (O₃). An imputation procedure for missing observations in the air pollution series was carried out in the Brazilian cities and results were compared before and after the imputation.

Results: Mean levels of PM₁₀ in these cities varied from 71.5 µg/m³ in Monterrey to 29.6 µg/m³ in Porto Alegre, while O₃ from 41.9 ppb in Sao Paulo to 14.1 ppb in Porto Alegre. Daily levels of air pollution were associated with mortality due to all causes in all ages for Sao Paulo and Rio with estimates slightly larger for Rio (RR for a 10 µg/m³ increase in PM₁₀ was 1.015 [95%CI 1.011-1.019]). No consistent effects were observed in Porto Alegre. In general, results for Santiago, Chile, showed smaller effects than for Brazilian cities (RR=1.003 (95%CI: 1.002-1.005) for a 10 µg/m³ increase in PM₁₀), while for people older than 65 the risk increases to 1.007 (1.005-1.010). For Mexican cities the RR for all causes/all ages mortality were 1.002 (95% CI 1.001-1.003) for Mexico City, 1.002 (95%CI 1.001-1.004) for Monterrey, and 1.005 (95%CI 1.001-1.008) for Toluca, and effects were observed mostly for deaths due to cardio-pulmonary and principally cardiovascular disease. In Brazil effects were observed in most cities for deaths due to respiratory diseases. Analysis performed in the series after the imputation procedure did not show any substantial changes in the results.

Conclusion: These results provide further evidence of the effects of air pollution in Latin America and can be used to estimate an overall effect of air pollution in the region with more precision. Other causes and age-groups will also be analyzed for individual cities and the second-stage analyses will combine results and explore the possible causes of heterogeneity.

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

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Introduction. The purpose of this project is to provide an understanding of the extent of coherence among findings of multi-city time-series studies of air pollution and mortality and hospitalization carried out in cities in North America and Europe. It sought to gain an understanding of the contribution of methodologic differences to variation of effect estimates in different studies; to characterize the extent of heterogeneity in effect estimates; and to evaluate determinants of heterogeneity. The APHENA project was based in data collected for the Air Pollution and Health: A European Approach (APHEA2) project in selected cities in Europe, the National Morbidity, Mortality, and Air Pollution Study (NMMAPS) in the 90 largest United States cities, and for multi-city research on the health effects of air pollution in Canada.

Methods. The project involved the initial development of analytic approaches for first-stage and second-stage analyses of the time-series data and the subsequent application of the resulting methods. The various investigative groups had used different approaches to the key issue of controlling for temporal confounding and there was a need to establish a standard protocol that would encompass prior approaches. The first-stage analysis used generalized linear models (GLM) with either penalized or natural splines to adjust for seasonality. For hospitalization data, the protocol took into account seasonal patterns, vacation effects, and increases with epidemics of respiratory disease. The second stage analysis used meta-regression approaches and assessed potential effect modification by sociodemographic characteristics and indicators of the pollution mixture. The two pollutants for which risks were estimated were PM_{10} and O_3 .

Result. In APHENA, the first stage results were robust to the choice of smoother and df used and generally replicated previous analyses by the three groups of investigators. For mortality and PM_{10} , risk estimates from the APHEA2 and NMMAPS databases were relatively close while estimates from the Canadian studies were substantially higher. For hospitalization, results did not contain discernable patterns of variation among the three datasets. PM_{10} effect modification patterns, explored only for cities with daily data, were not entirely consistent across centers. The levels of pollutants modified the effects differently in Europe and the U.S. and climatic variables were only important in Europe. In both centers, a higher proportion of older persons was associated with increased risk, as was a higher rate of unemployment. For O_3 and mortality the effects tended to be larger for the summer months and, in the U.S., to be diminished by control for PM_{10} . There was variation in the estimated effect of O_3 by df and across the three geographic regions. The effects of ozone on mortality were larger in Canada and there was little consistent indication of effect modification.

Conclusions. The APHENA project has shown that findings for mortality were generally comparable to those obtained previously and relatively robust to the method of analysis. For PM_{10} the effect modification pattern identified was not entirely consistent in Europe and the U.S. For O_3 there was no indication of strong effect modification.

Extrapulmonary Effects of Inhaled Ultrafine Carbon Particles in Mice

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Background: Exposure to particulate matter is associated with acute cardiovascular mortality and morbidity. The mechanisms involved in these effects are not fully elucidated. However it has been demonstrated that ultrafine particles are able to cross the alveolar-capillary membrane and translocate into the systemic circulation. Accordingly, systemic adverse effects of ultrafine particles have been explained either by release of soluble mediators from the lungs, and/or by the direct translocation of ultrafine particles into the bloodstream. In the here presented animal exposure study we test the hypothesis that translocated ultrafine carbon particles (UfCP) induce significant signs of extrapulmonary inflammation.

Approach and Methods: We compared systemic effects caused by two different exposure routes: whole body inhalation versus intra-arterial infusion, with the latter supposed to mimic only direct effects of translocated particles. Mice were either exposed to UfCP (440 µg/m³) or clean air for 4 or 24 hours by inhalation, or by intra-arterial infusion to the estimated dose of translocated UfCPs (5x10⁷ UfCPs). Mice were analyzed for systemic effects by automated haematology, multiplex plasma cytokine detection, and for organ specific effects by a panel of inflammatory markers (quantitative PCR and multi-analyte protein assay) in lung, aorta, heart and liver homogenates. In addition a FACS analysis for activation markers of peripheral mono- and granulocytes was performed.

Summary of Results: Only UfCP exposure by inhalation lead to a modest but significant proinflammatory response of the lungs. In contrast blood neutrophil and monocyte numbers increased especially after intra-arterial UfCP exposure, arguing for a particle induced recruitment of inflammatory cells. However solely inhalation exposure caused significantly reduced levels of blood leucocyte surface activation markers, possibly pointing to retention of activated cells via adhesion to stimulated endothelia. Also platelet cytograms uncovered only after inhalation exposure a mobilization and recruitment of platelets. Confirmatively we observed a decrease in blood fibrinogen levels and an increase in local fibrin deposition as detected by immunoblotting and immunohistochemistry in liver samples. At both, gene, and protein expression level, particle inhalation caused a stronger proinflammatory response as compared to infusion. Within the investigated organs heart, aorta and liver, the most notable changes in inflammatory gene expression were detected in aorta tissue.

Conclusion: Our results affirm that the inflammatory response in the lung is crucial for the expression of extrapulmonary inflammatory effects after exposure to UfCP. Consequently, from the lung to the bloodstream translocated UfCPs, mimicked by intra-arterial UfCP infusion, caused similar, but less pronounced changes of the investigated inflammatory endpoints in extrapulmonary organs like heart, aorta and liver. Hence, our data supports the hypothesis that a release of soluble mediators from the lungs or an activation of circulating blood cells in the capillary bed of the challenged lungs primarily drives the described particle related extrapulmonary effects. Our gene expression analysis revealed the most prominent inflammatory response in the aorta, which might point to a particular susceptibility of this organ.

Spatial Patterns of Particle-Bound PAHs and Fine Particulate in the Neighborhood of West Buffalo Adjacent to a Major Border Crossing

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Background. The Peace Bridge in Buffalo, NY is the third busiest U.S. crossing. On the U.S. side (Plaza), there are roads, custom inspection, passport control and duty-free shopping. About 5,000 diesel trucks and 20,000 cars cross daily, making it a “hot spot” for mobile source air toxins (MSATs). Particle-bound polycyclic aromatic hydrocarbons (p-PAHs) and ultra-fine particulates (UFP) were monitored in an abutting neighborhood to determine spatial patterns of these pollutants. Also, integrated samples (PM, black carbon, elements, volatile organic compounds (VOCs), carbonyls and PAHs) were collected at abutting upwind (Chapel) and downwind (Great Lakes Center (GLC)) locations. This poster will focus on the spatial patterns of p-PAH and UFP.

Methods. To define spatial patterns of UFP and PAHs, monitors in backpacks were carried by staff walking along established routes, including the Birdwalk pier which was 50 m to 100 m offshore in the Niagara River. Each backpack contained a P-Trak (TSI, Inc), a PAS2000CE (EcoChem), and a Vista GPS (Garmin). Sampling was conducted over two fourteen-day periods in the summer of 2005 and the winter of 2006. Data (over 80 hours) from both seasons were combined and parsed into two conditions: “lake” and “city” winds. “Lake” represented periods when the wind came from Lake Erie through the border crossing and into the neighborhood. “City” represented periods when the wind came from the city through the neighborhood and over the border crossing. ArcGIS software was used for exploratory analysis.

Results. “City” and “lake” wind conditions resulted in different concentration patterns. Mobile source PAHs, VOCs, elements and black carbon were elevated downwind of the Plaza. The patterns for “lake wind” are similar for winter and summer and morning and afternoon. UFP counts at the Chapel exceeded the UFP counts at the GLC by more than 10,000 p/cc more than 25 percent of the time and more than 20,000 p/cc more than 10 percent of the time, indicating a direct influence of bridge-related traffic. The p-PAH values at the chapel site exceeded the GLC site more than 70 percent of the time.

For Lake winds UFP for the Birdwalk averaged 7,000 p/cc while the UFP in the three nearest streets to the Plaza averaged three times higher at 22,000 p/cc. Street-by-street analysis showed a pattern for both UFP and p-PAH that decreased with distance from Plaza. The gradient over eight streets (800 m) for UFP showed differences of over a factor of two and for p-PAH a factor of three. The two farthest streets had no significant difference in p-PAH concentration from the Birdwalk.

Conclusions. Plaza emissions have an influence on ambient air quality over a range of a few hundred meters. Traffic-related emissions were discernable over background for about 50 meters into the neighborhood. The mobile UFP and p-PAH monitoring with GPS was innovative demonstrating mapping of concentration contours to the sub-block level. Diesel emissions together with persistent wind directions allowed for interpretive pollution maps. Spatial and temporally resolved information on the distribution of p-PAHs is relevant to understanding exposures of MSATs.

***European Hot Spot of Air Pollution for PM_{2.5} and B[a]P: Ostrava, Czech Republic**

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Background. The Ostrava Region in the Northern Moravia (Silesia) is the most polluted region in the Czech Republic in terms of levels of particulate matter (PM₁₀ and PM_{2.5}) and carcinogenic polycyclic aromatic hydrocarbons (c-PAHs), such as benzo[a]pyrene (B[a]P). Sources of this pollution are industry (steel production, coke oven), traffic and local heating. In the most polluted district of Ostrava City, Bartovice, in the year 2007, PM₁₀ levels were 66 µg/m³ (daily limit of 50 µg/m³ was exceeded 214 times), and B[a]P levels were 8.8 ng/m³ (97% of measurements exceeded 1 ng/m³). The increase of air pollution was accompanied by an increase in diagnoses of asthma in children (up to 15 years) in the pediatric district of Bartovice (2001: 115 asthmatic children/1201 registered; 2003: 139/1181; 2005: 192/1133, and 2007: 281/1082, respectively).

Objectives. The aim of the project is to gain new knowledge on the mechanisms of the effects of complex mixtures bound on dust particles (c-PAHs and toxic metals) and volatile organic compounds (VOC) in the ambient air on humans in the most polluted area of the Czech Republic - the Ostrava region. New methods of toxicogenomics will be used to study these effects. The adverse effects of the atmospheric pollutants will be studied on different levels (molecular epidemiology studies, in vitro studies) and in different populations (city policemen, children). The mechanisms of action of the complex mixtures on the human genome will be studied by the analysis of gene expression profiles (RNA chips) and individual genetic susceptibility to the effects of toxic air pollutants (genetic polymorphisms).

Experimental design.

Study: Health status of children. Analyses of children's respiratory morbidity up to 6 years of age in polluted and less polluted parts of Ostrava City (1000 children in each group). Incidence of acute upper and lower respiratory airways morbidity, bronchial asthma, atopic dermatitis, and allergic rhinitis will be investigated.

Study: Bronchial asthma in children and biomarkers. In the most polluted part (Ostrava-Bartovice) 100 children diagnosed with bronchial asthma and 100 healthy children, aged 8-12 years, will be selected. The following biomarkers will be evaluated: genetic polymorphisms (metabolic and DNA repair genes by RT-PCR), gene expression (toxicologically significant genes by Illumina chips), 8-oxodG, lipid peroxidation, oxidation of proteins, vitamins, and cotinine.

Study: Response of human cells to complex mixtures in vitro. Analysis of DNA adducts, oxidative damage, gene expression changes and protein expression changes by organic and inorganic extracts from particles collected in various localities.

Study: Molecular epidemiology study. In Ostrava City, 60 city policemen will be selected from polluted parts of the city and 60 policemen from less polluted parts and sampled repeatedly during two winters and one summer. Exposure to PM_{2.5}, c-PAHs, VOC and toxic metals will be assessed by stationary monitoring and c-PAHs and VOC by personal monitoring. The following biomarkers will be evaluated: DNA adducts, gene mutations, chromosomal aberrations, 8-oxodG, lipid peroxidation, oxidation of proteins, genetic polymorphisms (metabolic and DNA repair genes), gene expression profile, protein expression, vitamins, and cotinine.

* Study not funded by HEI.

Development of a Personal Exposure Aerosol Screening Model (PEASM) for Size-Resolved Urban Aerosols: Model Architecture and Study Objectives

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Background: Exposure models are important tools for explaining the causal pollutant components driving associations between ambient particle mass (e.g. PM_{2.5}) and morbidity and mortality. Two classes of pollutant components receiving recent attention as causal components are (a) gases and particulate matter (PM) from combustion sources, particularly from vehicles; and (b) ultrafine particles (UFPs) with sizes less than 0.1 µm, which have high pulmonary deposition efficiencies and high surface areas for effective delivery of adsorbed and condensed toxins with associated oxidative stress and inflammatory response. Quoting a 2005 review article, "...there is sufficient reason to believe that ultrafine particles are important in morbidity and mortality associations otherwise attributed to larger-size fractions" (Delfino, Sioutas et al. 2005, EHP 113(8): 934-946). This presents a serious puzzle to the health effects community since outdoor PM_{2.5} and UFPs are not correlated in many locations, and are often anticorrelated.

Since these causal agents occur in urban locations with sharp gradients in pollutant concentrations, high spatial-temporal resolution is required for both model- and measurement-based approaches at quantification. That fact, plus the explosion in gas and size-resolved PM measurements at urban scales and in dynamometer studies, gives motivation to the creation of a deterministic screening model for estimation of personal exposures at high spatial resolution. While studies of this general type exist, several features make the current effort unique: integration of the exposure model with recent health effects studies; simultaneous prediction of UFPs from combustion and from photochemical new particle formation; and allowance of external mixtures created from aerosol dynamical processing of combustion exhaust.

Objectives: In a recently initiated HEI-funded project, a Personal Exposure Aerosol Screening Model (PEASM) will be developed. The model will receive background aerosol size distribution and gaseous pollutant concentration from Community Multiscale Air Quality (CMAQ)- Model of Aerosol Dynamics, Reaction, Ionization and Dissolution (MADRID) and include detailed aerosol dynamic calculations. Computational burden will be managed by solving detailed aerosol dynamics at high spatial resolution only where necessary to calculate concentrations at receptors. Its utility for reducing exposure misclassification will be tested versus data from Southern California (Delfino, Sioutas et al. 2005, EHP 114(11): 1736-1743) and the correlation between model-predicted variables such as UFP concentrations and measured health effects will be evaluated.

Project Plan: Having begun this research as a 3 year effort commencing in December 2007 under HEI funding, the project is still in the initial phase of selecting computational and algorithmic approaches for the necessary model calculations. Aspects under detailed consideration during the first project year (2008) are: (1) fuel-based size-resolved emission factors; (2) integration of traffic activity and road network data into gridded emissions; (3) integration with CMAQ-MADRID for specification of upwind boundary conditions; and (4) development of integrated dilution/dispersion models (based on CALINE4 for roadway sources) with the aerosol dynamics model.

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

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Introduction: Air pollution both outdoor and indoor is of concern for developing countries. With rapid urbanization and industrialization, air pollution is increasing in many Indian cities. Air pollution levels in most of the mega cities in India exceeded the respective air quality guidelines recommended by the World Health Organization (WHO), which in turn affects human health adversely. Particulate matter is the pollutant of concern in many Indian cities, particularly in Delhi-the capital city. In recent years, several actions have been taken to address the growing air pollution problem in Delhi and other Indian cities, 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 evidence 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 (Public health Air Pollution in Asian cities) program.

Methodology: The study uses a retrospective time series data (3 years data) on air quality and registered data of naturally occurring deaths in Delhi, to study the change in daily death rate due to change in air quality levels. The methodology involves collection of: (i) data on ambient air quality for major pollutants for all monitored stations for the period of 2002 – 2004 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 and Implications: The present study findings show increase in particulate matter with 10 micron size cut off (PM_{10}) and Oxides of nitrogen (NO_x) were associated with increase in all cause natural deaths. It was found that for every 10 microgram per cubic meter change in PM_{10} was associated with only 0.11 percent increase in total all cause natural deaths. When oxides of nitrogen (NO_x) alone was considered in the model, daily deaths increased 0.85 percent for every 10 microgram per cubic meter increase in NO_x concentration. No significant impact was observed for changes in sulphur dioxide (SO_2) pollution. The study helps to better understanding the link between air pollution and health in local population and adds knowledge to the existing science.

Integrated Epidemiologic and Toxicologic Cardiovascular Studies to Identify Toxic Components and Sources of Fine Particulate Matter

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Background: It is not known which components and sources of fine particulate matter (PM_{2.5}) are most detrimental to human health. We are carrying out an integrated program of cardiovascular research that combines observational epidemiology and animal toxicology for the purpose of identifying the chemical components of ambient PM_{2.5} that contribute to the effects of long-term exposure on development and progression of atherosclerosis and incidence of cardiovascular events.

Methods:

1. Epidemiology. Two large ongoing cardiovascular population (cohort) studies, the Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air) in six cities and the Women's Health Initiative Observational Study (WHI-OS) in 40 cities, are being used to identify effects of long-term exposure to PM_{2.5} components on: (1) the extent of atherosclerosis as measured by thickness of the carotid arterial wall (carotid intima-media thickness = CIMT) and the amount of coronary artery calcification (CAC); and (2) the incidence of cardiovascular events. Cardiovascular risk factors and health endpoints in both cohorts (6,600 participants in MESA Air and 90,000 women in WHI-OS) are much better characterized than in other cohorts used to study air pollution effects on cardiovascular disease. Individual-level residential concentrations of PM_{2.5} chemical components and potential of PM to cause oxidant injury are being estimated using data from the nationwide fine PM_{2.5} speciation networks and intensive supplemental monitoring in MESA Air cities undertaken specifically for this project.

2. Toxicology. Based on the contrasting PM_{2.5} chemical component profiles in different regions of the country, well-characterized, laboratory-generated, inhalation exposures are employed in an animal model using a hyperlipidemic mouse that is very susceptible to atherosclerosis (Apo E knock-out) to directly test hypotheses on the long-term cardiovascular toxicity of motor vehicle emissions, secondary inorganic aerosol and fugitive dust, as well as combinations of these components. Effects of the gas phase portion of vehicle emissions alone and in combination with particulate components will also be tested. Morphologic, biochemical and functional endpoints of chronic cardiovascular effects that integrate well with the outcomes studied in the cohort studies will be examined in the animal model. This particular toxicological approach is well-suited to the task of directly identifying and comparing the components of PM_{2.5} that are suspected, based on our epidemiologic findings, of having the most cardiovascular toxicity.

Progress: As we begin the second year, we continue to concentrate on collecting and analyzing our enhanced PM_{2.5} component monitoring data in the MESA Air cities. The final round of two-season home sampling is nearly complete. Our pilot traffic exposure models perform better than traditional traffic exposure methods in characterizing local roadway gradients in pollutant concentrations.

Significance: The regulatory significance of this project is substantial. Identification of the most toxic components of PM, and of the corresponding sources of these components, will enable more focused and efficient approaches to regulating PM.

Induction of 1,2:3,4-Diepoxybutane-Specific Hemoglobin and DNA Adducts in Mice and Rats Exposed to 1,3-Butadiene

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Background. Butadiene (BD) is a high-volume industrial chemical and environmental pollutant for which human evidence, though limited, suggests the possibility that this agent causes lymphohematopoietic cancers in high-exposure occupational settings. Genotoxicity studies of BD in rodent models indicate that species differences in tumorigenic responses, where the mouse is far more susceptible than the rat, are largely related to the comparative formation of three DNA-reactive epoxides, including the highly mutagenic metabolite 1,2:3,4-diepoxybutane (DEB). The need for improved extrapolation between various rodent and human studies has led our research team (i) to determine if DEB-specific hemoglobin and DNA adducts are produced in rodents and man and (ii) to extend data for biomarkers of exposure down to 10% of the current OSHA occupational standard of 1 ppm BD.

Methods. Across three inhalation studies, B6C3F1 mice and F344 rats were exposed for 2 weeks to 0, 0.1, 0.5, 1.5, 6.25, 62.5, 200, or 625 ppm BD for ascertaining *in vivo* adduct formation and defining dose-response curves for DEB-specific hemoglobin and DNA adducts. An immunoaffinity liquid chromatography tandem mass spectrometry assay was used to measure N,N-(2,3-dihydroxy-1,4-butadiyl)-valine (*pyr*-Val) hemoglobin adducts in mice and rats. HPLC-ESI⁺-MS/MS methods were used to measure (i) N7-guanine—N7-guanine crosslink adducts (1,4-bis-(guan-7-yl)-2,3-butanediol) (*bis*-N7G-BD) in livers of BD-exposed mice and rats and (ii) 1-(Guan-7-yl)-4-(aden-1-yl)-2,3-butanediol (N7G-N1A-BD), one of four regioisomeric guanine—adenine crosslink adducts formed by *in vitro* reaction of DEB with DNA, in livers of BD-exposed mice.

Results. Comparisons of the resulting *pyr*-Val data and those for N-terminal valine adducts associated with formation of other epoxy intermediates show that BD metabolism is species and concentration dependent. Mice formed much higher amounts of *pyr*-Val than rats at similar exposures, and the efficiency for adduct formation was greater at low-level BD concentrations. Analysis of liver DNA from animals exposed to 0, 62.5, or 625 ppm BD showed species- and dose-related differences in the formation of *bis*-N7G-BD, with levels of racemic *bis*-N7G-BD being 11-fold higher in mice than rats at 625 ppm BD but only 4-fold higher in mice than rats at 62.5 ppm BD. In BD-exposed mice, formation of racemic *bis*-N7G-BD was 10- to 12-fold higher than formation of *meso bis*-N7G-BD. DNA from control mice and rats did not contain either *bis*-N7G-BD lesion. Liver DNA from mice exposed to 625 ppm BD, but not control mice, had measurable levels of N7G-N1A adducts.

Conclusions. The overall data generated thus far show clear species differences in the metabolism of BD to DEB, and provide compelling evidence that formation of DEB may be the major factor responsible for the differential susceptibility of BD-induced carcinogenesis in rodents. Particularly, DEB-induced *bis*-N7G-BD and N7G-N1A-BD crosslinks may contribute to BD-related mutagenesis at GC and/or AT base pairs *in vivo*.

Impact of the 1990 Hong Kong Legislation for Restriction on Sulfur Content in Fuel: An Approach Modeling the Relationship Between Mortality and Air Pollution Taking Account of Past Exposures

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Background: On July 1, 1990 the Hong Kong Government restricted the sulfur content of fuels to 0.5% by weight, as compared to the previous levels of up to 2.5%. Analyses of mortality following this intervention indicated that the reduction in death rates occurred. However, uncertainty remains about the independent effects of individual pollutants: on whether the effects seen in Hong Kong were related to the concomitant change in particulate composition, and whether there had been a long term benefit that is significant for public policy.

Objectives: We report preliminary development of our modeling approach of relationships between mortality and concentrations of the pollutants taking account the effect of past exposures. We then assess the model using the monthly all-cause mortality and pollutant data as an illustration.

Methods: We linked the ratio of reference death rate, $D_{ref}(t)$ (death rate that would have been observed in the absence of the intervention) to the observed death rate, $D(t)$ to the effects of pollutant concentrations with past exposures incorporating a decay function on mortality by a nonlinear regression. Monthly data for mortality and pollutants were used, for the period 1985-1999.

Results: The parameters of the regression for all-cause mortality taking into account past exposures were 0.0092, 0.0076 and 0.0083 per 10 $\mu\text{g}/\text{m}^3$, for SO_2 , PM_{10} and O_3 respectively (all three coefficients being statistically significant), in a regression with all three pollutants. When only current concentrations were modeled, for the effects of pollutants on mortality the estimates were similarly to those assessed by time-series short term effect studies.

Conclusion: The results show a strong association of mortality with pollutants. Further investigations are currently underway to develop a methodology for quantifying the benefits of restricting the sulfur content of fuel in terms of years of life gained, and the relationship between short-term and long-term benefits due to improvement in air quality.

Public Health and Air Pollution in Asia (PAPA): A Multi-City Study for Short-Term Effects of Air Pollution on Mortality

CM Wong on behalf of PAPA teams

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Background: To meet its goal in assessing the health effects of air pollution across the key and often under studied areas, a Public Health and Air Pollution in Asia (PAPA) project was established among three cities in China and Bangkok in Thailand in the first phase, and another three cities in India in the second phase. Individual teams followed the guidelines under a common protocol for development of core models and assessment of the effects, taking into account city-specific conditions.

Objective: To assess the effects of air pollutants on mortality within each city and the combined effects among all the four cities in the first phase of this project.

Methods: Daily counts of mortality for natural causes in all ages, age-specific groups, and for cardio-respiratory diseases at all ages, were modeled by generalized linear model. Trend and seasonality, temperature and relative humidity using smoothers of *natural cubic spline*, day 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 autocorrelations of the residuals. The effects of daily air pollutant concentrations of PM₁₀, NO₂ and SO₂ (24 hour average), and O₃ (8 hour average) were estimated.

Results: Ambient concentrations for PM₁₀, NO₂, SO₂ and O₃ varied across the four cities with mean levels ranging from 51.6 to 141.8 µg/m³, 44.7 to 66.6 µg/m³, 13.2 to 44.7 µg/m³, and 36.7 to 85.7 µg/m³ for the four pollutants, correspondingly. Meta-analysis showed that the combined excess mortality per 10 µg/m³ (95% confidence interval) estimate for PM₁₀ average concentration of current and lag one day among the four cities was 0.6% (0.3 to 0.9%) for all natural cause mortality at all ages in random effects models. For gaseous pollutants the corresponding estimates were: NO₂ 1.2% (0.8 to 1.6%); SO₂ 1.0% (0.8 to 1.2%) and O₃ 0.4% (0.2 to 0.5%). In individual cities, the pattern of the concentration-response curves showed linear effects for PM₁₀, except in Shanghai; and for gaseous pollutants, except NO₂ in Bangkok and Hong Kong, and SO₂ in Hong Kong.

Conclusions: Effect estimates of particulate pollutant in Asian cities are comparable to or greater than those observed in most North American and West European cities despite big differences in the concentration levels, while those for gaseous pollutants in Asian cities are as high as, or higher. The methodology developed in the PAPA framework could be applied to other cities conducting air pollution studies. Further efforts to elucidate the effect of socioeconomic factors that might modify the effects of air pollution on mortality are warranted.

Diesel Exhaust Particles–Induced Acute Loss of Respiratory Neutral Endopeptidase

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Background. Neutral endopeptidase (*NEP*) is a key cell surface peptidase in maintenance of airway homeostasis and involvement of the development of pulmonary disorders including asthma, COPD, and lung cancer. Targeted disruption of the *NEP* locus in mice results in enhanced lethality to endotoxin, indicating a crucial protective role for *NEP*. However, little information is available about the effect of airborne particulate matter on airway *NEP*.

Methods. Induced sputum *NEP* and cross-shift spirometry were measured on twelve normal subjects (11 males and one female, ranging in age from 19-33 [mean 23.7 ± 4.3 years]) following diesel exhaust particles (DEP) exposure.

Results. During exposure, two respirable dust samples collected over a period of 66-68 minutes demonstrated concentrations of less than $100 \mu\text{g}/\text{m}^3$. Personal exposure to DEP, as measured by elemental carbon ($n = 12$) averaged 538 ± 512 (range 91-1800) $\mu\text{g}/\text{m}^3$. Exposure times averaged 89 (range 56-134) minutes. For a single experimental shift monitored for 60 minutes, peak concentrations for NO_2 and CO respectively were 1.5 ppm and 22 ppm. A significant increase in soluble *NEP* in sputum was observed with 31% average net increases when compared with pre-exposure. Pearson's correlation analyses indicated that changes in sputum *NEP* activity were significantly associated with DEP exposure. DEP exposure also induced a significant decline in forced expiratory volume in one second (FEV_1 , 4.03 ± 0.29 vs. 3.78 ± 0.29 ; $p = 0.005$ pre- vs. post exposure) and forced vital capacity (FVC, 5.16 ± 0.36 vs. 4.86 ± 0.39 , $p = 0.017$), which were significantly associated with sputum *NEP* activity.

Conclusions. This study revealed that there is acute loss of airway *NEP* activity after exposure of human volunteers to DEP, as indicated by increases of soluble *NEP* in sputum. Although the action mechanism underlying this effect remains to be determined, the change in *NEP* may be an important endpoint for DEP exposure, be mechanistically linked to related epidemiological findings, and indicate a greater susceptibility to the risk of pulmonary diseases.

The Beijing HEART Study — Health Effects of Air Pollution Reduction Trial

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Unprecedented actions will be taken during the 2008 Beijing Olympics and Paralympics (July 25 – September 17, 2008) to ensure that ambient air quality in one of the world's most polluted regions will be substantially improved. The targeted reduction in fine particulate matter (PM_{2.5}) is ~70% from a pre-Olympics level of >100 µg/m³. This study will take advantage of this unique opportunity to test the following hypotheses: (1) *Biomarkers of lung and systemic inflammation, vascular endothelial dysfunction, blood coagulation, autonomic dysfunction, and oxidative stress measured in local residents will change significantly in response to this substantial air pollution reduction. Further, these biomarkers will return to pre-Olympic levels following relaxation of air pollution controls when the Olympics are over.* (2) *PM_{2.5}, ultrafine particles, and certain PM constituents will each be associated with specific biomarkers across the whole study period.* (3) *Subjects' responses to changes in pollutant exposure will vary depending on their inherited polymorphisms for molecular pathways related either directly to the biomarkers measured or to mechanisms of PM-induced oxidative stress.*

This study will be carried out in 50 male and 50 female, healthy, non-smoking medical residents, who work and reside in the same hospital facility where both air pollutants and biomarkers will be measured. Specifically, we will: (1) measure PM constituents and co-pollutants on a continuous or daily basis throughout the three study periods (pre-Olympics, during-Olympics, and post-Olympics); (2) measure a suite of biomarkers reflecting lung and systemic inflammation, endothelial dysfunction, blood coagulation, autonomic dysfunction, and oxidative stress, in each subject twice per period (6 times total); (3) analyze candidate gene polymorphisms in each subject; and (4) perform statistical analyses to test the above hypotheses.

Epidemiological evidence strongly suggests that acute and chronic cardio-respiratory diseases and events are related to exposure to air pollution especially PM_{2.5}. However, specific mechanisms for these outcomes remain ill-defined; and mechanistic studies have been very limited and largely confined to laboratory-based exposures that may not reflect real-life conditions. By expanding the suite of PM constituent measures, measuring multiple biomarkers and pathway-related genes simultaneously, and examining a wide range of time frames (from hours to days to a few weeks) for biomarker responses, this real-world study is a comprehensive investigation of several prominently hypothesized mechanisms of PM effects. It will also provide invaluable data to improve the assessment of public health impacts of air pollution reduction.

This study is co-funded by NIEHS through an investigator initiated grant - # 1R01 ES015864-01A1

Activation of Endothelial Cells After Exposure to Ultrafine Particles

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Background. Although numerous epidemiological studies indicate a positive relationship between levels of ambient particulate matter (PM) and cardiovascular diseases (CVD), the cause of PM-induced CVD is still unclear. Vascular oxidative stress can damage endothelial cells and cause a vicious cycle of inflammation, thrombosis, and edema, thus playing a major role in conditions such as acute lung injury, and cardiopulmonary diseases. Recently, several studies have shown that ultrafine particles (UFPs) may pass from lungs to the circulation because of their very small diameter, and induce lung oxidative stress with a resultant increase in lung epithelial permeability. The direct effects of UFPs on vascular endothelium remain unknown.

Method. In this study, we collected UFPs using a nano-MOUDI cascade impactor in the Downtown Louisville area, Kentucky. To determine the chemical makeup in UFPs, 25 elements (C, N, O, S, Cl, K, Ca, Ti, V, Cr, Mn, Fe, Cu, Zn, As, Pb, Se, Rb, Sr, Mo, Na, Mg, Al, Si, P) were analyzed by means of particle induced x-ray emission (PIXE) and energy-dispersive X-ray fluorescence spectrometry. The size of UFPs were also analyzed by a JEOL JEM-2010 F field-emission analytical transmission electron microscope equipped with an Oxford EDS detector, a STEM (scanning TEM) unit and GIF/PEELS (Gatan Imaging Filter/Parallel EELS) system. The particle size and morphology were characterized from bridge field images recorded by a Gatan 794 slow-scan CCD camera. Our results confirmed that C, N, O, Al, Si, S, K, Ca and Fe are major elements in the UFPs from Louisville area. We determined the cytotoxicity effects and the ability of UFPs to generate reactive oxygen species (ROS) on mouse pulmonary microvascular endothelial cells (MPMVEC) *in vitro*.

Results. Our results showed that there were dose- and time-related cytotoxic effects and ROS generation after exposure to UFPs. Our results also demonstrated that UFPs caused MPMVEC activation and altered gene expression alternation. UFPs caused up-regulation of Jun-B, Akr1b8, Egr-1 and PAL-1 gene expression in MPMVEC.

Conclusions. Our findings strongly suggest that UFPs can directly affect endothelial cells to generate ROS which can further cause altered gene expression.

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Assessing Children's Exposure to Ultrafine Particles from Vehicular Emissions

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Background. Although increasing evidence has demonstrated toxic effects of ultrafine particles (UFPs, diameter $< 0.1 \mu\text{m}$), related epidemiological studies are limited mainly due to the complexity of UFP exposure assessment. Unlike fine particulate matter ($\text{PM}_{2.5}$) which has a relatively homogeneous distribution within an urban air shed, UFP concentration changes rapidly as the distance from the emission source increases, thus making central monitoring station data of limited use for assessing its exposure.

Objectives. This study will focus on primary UFPs from vehicular emissions, which account for $>90\%$ of total UFPs in urban environments, and focus on a sensitive sub-population, school children who have immature respiratory systems and faster breathing rates. The objective of this study is to identify hot spots where school children are likely to be exposed to high levels of UFPs and develop simple models to estimate children's exposure to UFPs from vehicular emissions. The central hypothesis is that school children are exposed to high levels of UFPs during school bus commute and inside and outside the classroom near major roadways.

Previous Studies. While previous studies have quantified school bus in-cabin air pollutant concentrations, research that specifically focuses on the impacts of retrofit devices on in-cabin diesel-related pollutant concentrations is limited. There are only two buses that were tested both before and after installing retrofit devices, one in Atlanta and one in Ann Arbor. The small sample size makes it difficult to draw reliable conclusions about the impacts of retrofit devices on in-cabin pollutant concentrations. Furthermore, in previous studies, UFP, a major component from diesel emissions, was either not investigated or monitored with a hand-held P-trak monitor which only measures down to about 25-40 nm and misses a significant portion of UFPs from vehicular emissions.

Experimental Design. In this study, number concentration and size distribution of UFPs, PM_{10} , $\text{PM}_{2.5}$, carbon monoxide, black carbon, and nitrogen oxide concentrations will be monitored 1) inside six diesel-powered school buses before and after installing retrofitting devices while driving on various routes and 2) inside and outside five classrooms at increasing distances from major roadways. Special considerations are taken in the study design to maximize the variance of traffic emissions, atmospheric dispersion, and bus or classroom ventilation settings to ensure the detection of their potential association with UFPs. At the completion of the study, major factors that influence school children's exposure to vehicular emitted UFPs will be identified and simple models will be achieved to reliably predict UFP concentrations in studied microenvironments. This will provide guidance to implement institutional controls to reduce children's exposure to vehicular emitted UFPs and facilitate future studies that focus on UFP health effects.

Atmospheric Transformation of Diesel Emissions

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Background We hypothesized that atmospheric transformation of diesel exhaust (DE) would change DE composition and toxicity. The specific aims were: (1) to characterize the gas- and particle-phase products of atmospheric transformations of DE under the influence of sunlight, ozone, and hydroxyl and nitrate (NO₃) radicals; and (2) to explore the changes in biological activity of DE under the same conditions.

Methods DE was generated on-site at the EUPHORE simulation chamber in Valencia, Spain using a light-duty modern rail direct injection, turbocharged, intercooled diesel engine and modern diesel fuel (47 ppm sulfur and 15% aromatic content) mounted on a dynamometer system equipped with a Horiba continuous gas analyzer. The test matrix included effects of atmospheric aging and NO₃ radical reactions in the dark and photooxidation and hydroxyl radical reactions in the sunlight on the DE composition, with or without addition of volatile organic compounds (VOC). Particulate matter (PM) and semi-VOC (SVOC) were collected from the chamber for chemical analysis at the end of the exposures, using an XAD-coated annular denuder followed by a Teflon-impregnated glass fiber filter and an XAD cartridge. Parallel samples for toxicity evaluation were collected using Teflon filters followed by two XAD cartridges. Unrealistically high levels of nitrogen oxides (NO_x) in the chamber following the first campaign required the development of a NO_x denuder, which was used during DE injection in the following two campaigns (total, 3 campaigns). Particle size, number, and volume concentrations were analyzed with a Scanning Mobility Particle Sizer. Ozone, NO_x, and NO_y species were monitored using chemiluminescence and Fourier Transfer Infrared instruments. Chemical analyses included determination of sulfate/nitrate, organic/elemental carbon fractions, and organics (polycyclic aromatic hydrocarbons [PAH], nitro-PAH, polars, alkanes, hopanes/steranes). The biological activity of the extracted PM + SVOC was evaluated by intratracheal instillation in rodents (rats for the first two campaigns and mice for the third, due to the small amounts of sample available) followed by evaluation of pulmonary toxicity, inflammation, and, in mice, oxidative stress responses.

Results All light exposures and NO₃ radical dark exposures formed additional particles and SVOC mass due to reactions of VOC, SVOC, and inorganic gases. The greatest increase in mass occurred with the addition of VOC as co-reactants. The organic mass formed increased the proportions of pyrolyzed organic carbon fraction, suggesting formation of very polar and oligomeric compounds. Toxicity data are consistent with the hypothesis that the biological potency of samples collected from these atmospheres is affected by changes in composition. These changes resulted from both atmospheric aging conditions and changes in composition presumably associated with aging of the engine.

Conclusions Chemical composition varied markedly with both the age of the engine and the presence of co-reactants. Toxicity also varied significantly among the samples. Generalizations are difficult for several reasons, including the different species used for toxicity testing, alterations in the composition and toxicity of the baseline DE mixture, and in some cases, strikingly non-monotonic dose-response relationships. However, there appeared to be trends towards increased toxicity under conditions where hydroxyl radicals or additional VOCs were present.

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