CENTER FOR CLEAN AIR RESEARCH
UNIVERSITY of WASHINGTON
Department of Environmental and Occupational Health Sciences

University of Washington CCAR Year 2 Annual Progress Report

Reporting Period: December 1, 2011 – July 31, 2012

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Center Name: UW CCAR, Center for Clean Air Research
Center Director: Sverre Vedal

Collaborating Institutions	Location
University of Washington	Seattle, WA
Washington State University	Pullman, WA
Lovelace Respiratory Research Institute	Albuquerque, NM
University of New Mexico	Albuquerque, NM

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REPORT OVERVIEW

This Annual Progress Report covers the second year of funding to date [12/1/2011 – 7/31/2012] for the University of Washington's Clean Air Research Center, termed the "UW CCAR - Center for Clean Air Research."

Each of the four individual EPA Clean Air Research Centers aim to advance understanding of the human health effects of exposures to complex (multipollutant) air pollution mixtures. The UW Center, specifically, is examining how pollution from roadways affects cardiovascular health. The research integrates exposure, epidemiological, toxicological, clinical, and statistical sciences to study the cardiovascular hazards of recent and aged roadway emissions.

The Center consists of two core function groups providing biostatistical analysis support and administrative activities. There are four separate institutions, contributing to five distinct but integrated research projects, with a sixth project being carried out in the Biostatistics Core. The projects and core groups are listed below and will be expanded on in individual summaries. Center investigators and their respective institutions will be listed with their associated research projects.

The individual project summaries review objectives and report on changes or difficulties encountered during the reporting period. Progress and preliminary results, as well as discussion about future activities, are included. The Administrative Core summary serves as the overall Center review. Additionally, there is a separate financial report, which provides a more detailed summary of the Center's financial picture to date.

Research Projects & Core Groups:

- Administrative Core
- Biostatistics Core
- Project 1 - Exposure Mapping – Characterization of Gases and Particles for Exposure Assessment in Health Effects and Laboratory Studies
- Project 2 - Simulated Roadway Exposure Atmospheres for Laboratory Animal and Human Studies
- Project 3 - Cardiovascular Consequences of Immune Modification by Traffic-Related Emissions
- Project 4 - Vascular Response to Traffic-Derived Inhalation in Humans
- Project 5 - Effects of Long-Term Exposure to Traffic-Derived Aerosols and Gases on Subclinical Measures of Cardiovascular Disease and DNA Methylation in a Multi-Ethnic Cohort

ADMINISTRATIVE CORE – CENTER REVIEW

Member	Institution
Sverre Vedal – Center Director	University of Washington
Jacob McDonald – Center Deputy Director	Lovelace Respiratory Research Institute
Timothy Larson - Center Deputy Director	University of Washington
Amanda Gassett – Center Quality Assurance Manager	University of Washington
Mark Davey – Center Manager	University of Washington

Objective of Research

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

The Center consists of five highly integrated research projects and two facility cores that together are pursuing the following six aims:

1. To characterize real-world near-roadway pollutant concentrations, particle size distributions and chemical composition

2. To simulate realistic contrasting near-roadway multi-pollutant exposure atmospheres for laboratory animal and human studies

3. To identify cardiovascular and immunologic effects and the pathogenic mechanisms of near-roadway exposures using animal models

4. To identify cardiovascular and immunologic effects of near-roadway exposures in human clinical studies

5. To identify effects of long-term exposure to traffic-derived particles and gases on sub-clinical measures of cardiovascular disease and DNA methylation in a multi-ethnic population

6. To develop a statistical and methodological framework for studying health effects of multi-pollutant mixtures

Progress Summary / Accomplishments

Committees and Meetings

- Investigators Committee – The Investigators Committee is comprised of key members from all five research projects, as well as representatives from the Biostatistics and Administrative Cores. As the research activity has accelerated in Year 2, this group now meets approximately every four weeks for status reports and to discuss the day to day scientific activities of the Center and its individual projects. We have also initiated a results or discussion period in these meetings where, on a rotating basis, investigators from each project present findings and progress.

- Internal Steering Committee – The Internal Steering Committee (ISC) is comprised of the Center Director, Deputy Directors, project and core PI's, the Center Quality Assurance Manager (QAM), and the Center Manager. This group meets quarterly to discuss finances, budgets, resource allocation, and collaborations. The ISC also serves as the Cross Collaboration Committee and convened recently to discuss the inter-Center collaboration projects proposed during the June 2012 CLARC Annual Meeting. The projects and scientific components of interest, collaborating parties, and budgeting requirements were discussed and the recommendations from this meeting are included in the Annual Report to help define the Center's collaborative focus and participation.

- Scientific Advisory Committee – The Scientific Advisory Committee (SAC) is composed of ten scientists representing varying specialties and institutions, including the US EPA and members from the other CLARC Centers. A list of the committee members with their associated institutions appears in Table 1. The committee convened in Seattle for the first annual "UW CCAR" SAC meeting on September 26th and 27th 2011. We thank the committee for evaluating our Center's initial project plan and for sharing their ideas. The insight and suggestions provided during that meeting, and in the follow up SAC comments, were greatly appreciated and have been strongly considered by our investigators. Our second SAC committee meeting is scheduled for September 27th and 28th 2012 with a similar format to the previous year. All ten members, as well our EPA program and project officers, have confirmed their attendance and are expected to participate and offer constructive advice on the Center's progress, direction, focus, and future.

Table 1 – CCAR Scientific Advisory Committee Members

Expertise	**Member**	**Institution**
Exposure Science	Michael Brauer	University of British Columbia
Exposure Science	Thomas Peters	University of Iowa
Exposure Science	Barbara Turpin	Rutgers University
Epidemiology	Arden Pope	Brigham Young University
Toxicology	Ian Gilmour	US EPA
Toxicology	Jake Lusis	University of California, Los Angeles
Toxicology	Sanjay Rajagopalan	Ohio State University (Michigan State University CLARC Member)
Statistics	Brent Coull	Havard University (Harvard University CLARC Member)
Clinical Studies	John Balmes	University of California, San Francisco (Chair)
Clinical Studies	Nicholas Mills	University of Edinburgh, UK

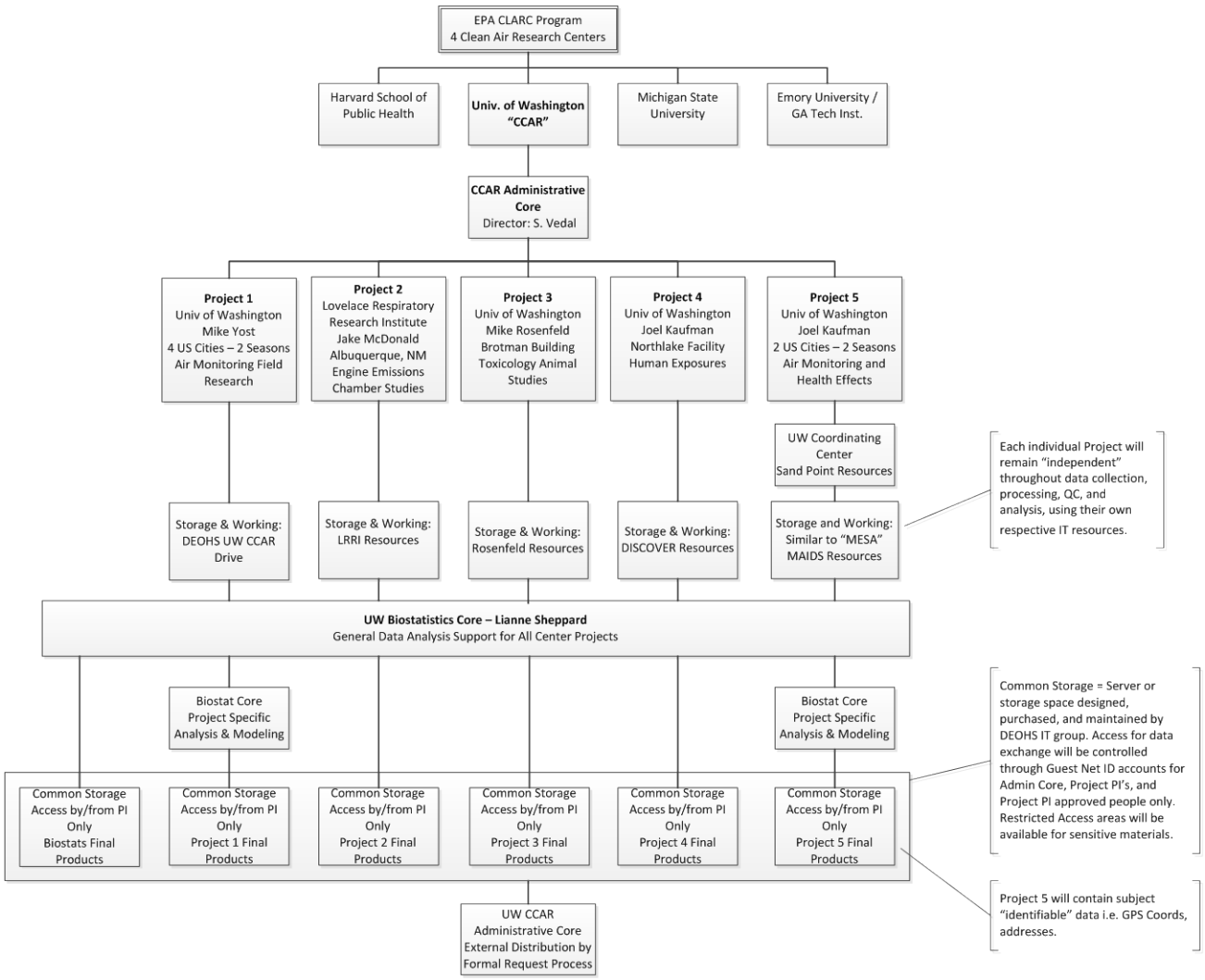
Information Technology

- The Center continues to utilize the University of Washington's Department of Environmental and Occupational Health Sciences (DEOHS) temporary server space. This resource is appropriately maintained, secured, and archived by DEOHS IT personnel, with password access for approved Center/project personnel. Its capacity is adequate for the current usage and can be expanded if needed.

- Each of the lead investigators, as well as the Internal Steering Committee, has been consulted for their data storage preferences and requirements, through the end of the Center's award period. It was determined that the most appropriate course would be to have each project collect, process, analyze, and store their respective raw and "intermediate" data on their own institution or research group IT resources. Final products, or output from each project, and from the Biostatistics Core, will be stored for inter-project use, as well as external use and distribution, on a common Center drive. This drive would be password accessible to only the project PI's and those approved by them. A Structured Query Language (SQL) server, as previously considered, will not be necessary. The proposed drive will integrate into an existing University of Washington DEOHS system, providing a very cost effective, flexible, reliable, protected, and secure computing environment that can be expanded and reconfigured easily. Figure 1 provides a general overview of the proposed project and data structure.

- The Center's web site has been live for almost one year and continues to provide information to the investigators, as well as to the general public. Content relating to the Center's calendar members, projects, and collaborators remains current. This Year 2 Annual Report provides a comprehensive list of all publications, presentations, posters, etc. relating to Center activities and these items will populate the site as soon as possible. As the Center and its individual projects continue to progress, we expect to have significant content to add to the Web site.

Figure 1 – CCAR Proposed Project and Data Structure



Subawards

- The three original Center subawards for Washington State University, Lovelace Respiratory Research Institute (LRRI), and the University of New Mexico were renewed for Year 2. We appreciate their participation and contributions to the Center as the research progresses. Financial information relating to the subawards can be found in the separate Center Annual Financial Report.

Difficulties Encountered and Revised Goals

Note: Individual project summaries detail any difficulties encountered, or revisions of originally proposed goals or activities.

- Overall, the Center has been on schedule with no major difficulties through the Year 2 award period.

- A continuing goal for the Administrative Core is to provide better communication with the individual projects, as well as the subawards. The physical distance between many of the investigators, facilities, and institutions can often present coordination challenges. This applies to financial status reports, reinforcing documentation requirements, maintaining quality objectives, and promoting a continual process of review and revision of procedures. With operations becoming more routine across the Center, standard meeting times have been established, along with better defined roles and expectations for the investigators and their respective teams.

- As the research progresses and significant data is collected, there will be a heightened effort to promote the expertise of the Biostatistics Core to all of the individual projects. The Biostatistics Core has their respective aims, but was also created and structured to be a Center resource for consultation and review of questions, materials, methods, and processes. It is anticipated, and expected, that all of the projects and investigators will rely heavily on the Biostatistics Core during the data intensive second half of the Center's award period.

Problems, Delays, Adverse Conditions

There have been no significant problems, delays, or adverse events associated with any of the individual projects, or the Center as a whole. Less significant events will be covered within each individual project or core summary.

Changes in Key Personnel

There have been no changes in key personnel for this reporting period.

Unexpected Cost Increases

Unexpected cost increases and budget reallocations, as well as other relevant financial information, are detailed in the individual project summaries contained in the separate Center Annual Financial Report.

Quality Control / Assurance

- The Center Quality Management Plan (QMP) was submitted and approved within 60 days of the initial award by the EPA Quality Assurance Manager in March 2011. That document has been circulated to all Center personnel and resides on the Center server and public web site. There have been no revisions required to this document since the last August 13, 2011 submission. With the significant progress of Projects 1, 2, and 3, and the anticipated start of Projects 5 and then later 4, this document will shortly undergo a comprehensive review to confirm the currency of overall goals and objectives, training, procedures and systems, documentation, and data storage and security.

- Each individual research project's Quality Assurance Officer (QAO) is continually creating and revising Standard Operating Procedures (SOPs), as required, as part of an ongoing process to document all Center and project specific activities.

- The Center's Quality Assurance Manager (QAM) has worked closely with the three projects actively collecting research data. Projects 1, 2, and 3 have submitted Quality Assurance Project Plans (QAPPs) that have been reviewed, revised, and approved by the QAO. Projects 4 and 5 have received materials to create their QAPPs and will have their plans submitted and approved by the QAO before any analytical data is collected. When appropriate, the Biostatistics Core will be required to provide a QAPP, or similar plan, to fully document their activities. This plan will also be reviewed and approved by the Center's QAM.

Planned Activities for the Subsequent Reporting Period

The individual project and Biostatistics Core summaries will address planned and future activities.

<u>Administrative Core</u>

- Committee Meetings – The Investigators and Internal Steering Committees will continue to meet regularly to discuss and refine the direction of the Center. Coordination for the Sept. 27th and 28th SAC meeting is underway.

- Quality Management – The Center will continue to follow up with each individual project, and associated QAO, to review, revise, and archive all relevant SOPs, and their respective QAPPs. Additionally, Projects 4 and 5 will be responsible for submitting for approval their individual QAPPs before any data is collected.

- Information Technology – With the computing space for the Center, and each of its individual projects and cores now defined, the Center Manager will work with UW DEOHS IT staff to design and purchase the appropriate hardware needed to house the Center's drive for final working products. This process should be completed and the system functional before the new year of 2013.

Human Subjects & IACUC

Below is a summary of the Human Subjects and Institutional Animal Care and Use Committee (IACUC) status for each individual research project. The Center Manager has confirmed that all projects and personnel have the appropriate certifications and training required for Year 2, and beyond.

Administrative Core - All Human Subjects training and certifications are current and documented with the UW CCAR Manager, as of July 31, 2012. Institutional IACUC approval for the University of Washington and LRRI are on file with the Center Manager and the CLARC EPA Project Officer.

Biostatistics Core - There are no immediate Human Subjects or IACUC concerns for the Biostatistics Core.

Project 1 - There are no immediate or planned Human Subjects or IACUC concerns for Project 1.

Project 2 - There are no immediate Human Subjects or IACUC concerns for Project 2.

Project 3

University of Washington: IACUC Protocol #2650-08, February 24, 2011

- Significant change approval to Protocol #2650-08 for Biological Use Authorization (BUA) to add "Endotracheal Installation of C. Pneumonia to Mice" was submitted February 23, 2012, approved March 12, 2012, and is on file with the Center Manager.

Lovelace Respiratory Research Institute: IACUC Protocol #FY11-083, March 18, 2011

- Amendment A to Protocol #FY11-083 for adding one laboratory person was submitted for documentation purposes June 20, 2011 and is on file with the Center Manager.

- Amendment B to Protocol #FY11-083 for adding one new strain, C57B16, and 104 mice was submitted May 11, 2012, approved June 7, 2012, and is on file with the Center Manager.

Project 4 - Because the project's Human Subjects activities are not scheduled to begin until Year 3 of the Center, there are no immediate Human Subjects or IACUC concerns for Project 4.

Project 5 - The Center and Project 5 are currently working with the UW Collaborative Health Studies Coordinating Center (CHSCC) and the MESA Air field centers at UCLA and Wake Forest University to acquire the appropriate Human Subjects approvals for the personal and residential sampling, scheduled to begin January 2013 in Winston-Salem, NC. As the HSD agreements are already in place from previous MESA Air research, this should be a routine process of modifying the existing documentation. There are no IACUC concerns for Project 5. All documents will be on file with the Center Manager, when approved and available.

Publications / Presentations / Posters - Cumulative

The below publications, presentations, and posters are also included in their associated individual project summaries, where appropriate.

Center Publications to Date:

1. Campen MJ, Lund A, Rosenfeld M. Mechanisms linking traffic-related air pollution and atherosclerosis. Curr Opin Pulm Med. 2012 Mar;18(2):155-60. PMID: 22189455

2. Cosselman KE, Krishnan RM, Oron AP, Jansen K, Peretz A, Sullivan JH, Larson TV, Kaufman JD. Blood Pressure Response to Controlled Diesel Exhaust Exposure in Human Subjects. Hypertension. 2012 May;59(5):943-8. Epub 2012 Mar 19. PMID: 22431582

3. Szpiro AA, Sheppard L, Lumley T. Efficient measurement error correction with spatially misaligned data. *Biostatistics*, 2011a, 12:610-23.

4. Sheppard L, Burnett RT, Szpiro AA, Kim S-Y, Jerrett M, Pope CA III, Brunekreef B. Confounding and exposure measurement error in air pollution epidemiology, *Air Quality, Atmosphere & Health*, 2011, Jun;5(2):203-216.

5. Szpiro AA, Paciorek C, Sheppard L. Does more accurate exposure prediction necessarily improve health effect estimates? *Epidemiology*, 2011b, 22:680-685.

6. Vedal S, Kaufman JD. What does multi-pollutant air pollution mean? Am J Resp Crit Care Med 2011; 183: 4-6.

Center Presentations to Date:

1. CLARC Program Announcement - Society of Toxicology Conference (SOT) – March 2011 (Washington DC)

2. CLARC Program Kickoff Meeting - April 2011 (Raleigh, NC)

3. CLARC Program Annual Meeting – June 2012 (Boston, MA)

4. Szpiro AA. Exposure Model Selection in Air Pollution Epidemiology: Single and Multiple Pollutants. Clean Air Research Centers Annual Meeting. Boston, MA, June 2012.

5. Vedal S, Szpiro AA. Methods for Estimating Health Effects of Multipollutant Mixtures in Cohort Studies. ISEE Annual Meeting. Barcelona, Spain, September 2011.

Center Posters to Date:

1. Campen MJ, McDonald JM, Rosenfeld ME, Lund AK. Cardiovascular Consequences of Immune Modification by Traffic-Related Emissions. Clean Air Research Centers Annual Meeting. Boston, MA, June 2012.

2. Keller JP, Sheppard L, Szpiro AA, Sampson PD. Spatial Analysis of a Marker of Roadway Emission Aging. Clean Air Research Centers Annual Meeting. Boston, MA, June 2012.

3. VanReken T, Jobson T. Chemical Characterization of the LRRI Exhaust Exposure Chambers by PTR-MS and HR-ToF-AMS: Early Results. Clean Air Research Centers Annual Meeting. Boston, MA, June 2012.

Supplemental Keywords

Atherosclerosis, Epidemiology, Toxicology, Transportation

Relevant Web Sites

http://depts.washington.edu/uwccar/

INDIVIDUAL PROJECT/CORE SUMMARIES

Biostatistics Core

Investigator	Institution
Elizabeth A. (Lianne) Sheppard	University of Washington
Paul Sampson	University of Washington
Adam Szpiro	University of Washington

Objective of Research

The overall objective is to support the statistical needs of all Center projects. This will be achieved through five specific objectives:

1. Advise Center projects on data management and compilation. This Core will provide advice on database design, forms design, data entry support, data quality review, data storage, back-up and documentation.

2. Ensure quality statistical design and analysis of Center research. The Core members meet regularly (weekly); these meetings ensure regular attention to the vast array of (bio)statistical needs of the Center, including: study design, power calculations, data collection, statistical analysis plan development, statistical analysis, and interpretation of results.
3. Implement novel statistical methods that are required for Center projects. Novel statistical methods are incorporated into Projects 5 and 1 to jointly model and then estimate health effects for mixtures of pollutants.

4. Identify additional statistical methodological research that will advance Center projects and seek resources to perform such research. The active participation of statisticians in the scientific research of the Center enables identification of innovative statistical methods and approaches to statistical analyses to deal with the most pressing scientific needs of the Center. The Center will catalyze (but not fund) solicitation of resources for new methodological research.

5. Communicate and disseminate Center findings. This Core will aid in the interpretation of Center findings and use examples from Center research in statistical papers on methodological development and implementation. The Core will also collaborate on manuscripts, foster understanding of statistical methods, and engage statisticians in air pollution research.

Progress Summary / Accomplishments

The primary activities to date of the Biostatistics Core have fallen in three areas: participation in overall UW CCAR and CLARC activities, supporting the design and data management of the mobile monitoring research being conducted by Project 1, and advancing statistical methodological research.

Overall UW CCAR and CLARC Activities

Drs. Sheppard, Sampson, and Szpiro attended the June CLARC meeting along with student Josh Keller and soon-to-be-hired postdoctoral fellow Roman Jandarov. All Core representatives participated in the CLARC Biostatistics Workshop with presentations by Drs. Sheppard, Szpiro, and Sampson. This Core has collaborated with other Centers to develop two collaborative proposals: one on multipollutant measurement error, the other on modeling pollutant fields using satellite data.

Support of Project 1

The monitoring campaigns being conducted by Project 1 involve two different activities in each of four cities: 1) a mobile monitoring campaign that includes both continuous monitoring at a single fixed site along with repeated sampling of multiple intersections along 3 pre-determined routes over 9 days within a two-week period during afternoon rush hours, and 2) a concurrent passive sampling campaign at a fixed number of stationary sites for a two-week period. Biostatistics Core faculty and staff continue to support enhancements to the design of the monitoring campaigns. This year the Core has also supported a wide range of data-related activities including data cleaning, management, analysis, and presentation. We have recently begun to fund additional staff to develop the Project's database management system.

Advancing Methodological Research

Our methodological work is advancing on two fronts: developing approaches to predict multipollutant surfaces across space and estimation of multipollutant health effects. Our objective is to use full multipollutant monitoring data to obtain estimated multivariate eigenpollutant health effects. (As described in our proposal we call eigenpollutants mixtures of multiple pollutants determined by a principal component analysis.)

1. Mutipollutant Prediction: In our current work we are considering whether the data reduction necessary to estimate eigenpollutants should be done prior or after to predicting pollutants. This project will move more quickly once our postdoctoral fellow starts in September.

2. Mutipollutant Health Effects: It is now well understood that spatial misalignment of exposure and health data means that a statistical model needed to predict exposures at subject locations (e.g. Sheppard et al 2011). Less attention has been paid to the implications of the predicted exposures in the inference about health effects. We have shown that counter to intuition, the best exposure model for prediction accuracy is not always the best for health effect inference (Szpiro et al 2011b). We have also developed theory to decompose the measurement error into Berkson-like error (from smoothing) and classical-like error (from estimating smoothing parameters) and have clarified the tradeoffs between these Berkson-like and classical-like components (Szpiro et al 2011a). Recent work suggests that for single pollutants 1) a lower rank exposure model increases Berkson-like error but decreases classical-like error; this may improve health effect inference even at the cost of worse prediction accuracy, and 2) it may be reasonable to guide the exposure model selection (e.g., lasso parameter selection) by the asymptotic results for health effect parameter estimates rather than prediction. Our preliminary assessment of mutipollutant effects has shown that incompatibility between exposure models for different pollutants can introduce bias in the health effect estimates from the Berkson-like error component. Further work is needed to understand how to correct for this bias; we believe that the tradeoff with variability from classical-like error may depend on whether compatible models will work "almost as well" for individual pollutants.

Publications / Presentations / Posters

Publications

1. Sheppard L, Burnett RT, Szpiro AA, Kim S-Y, Jerrett M, Pope CA III, Brunekreef B. Confounding and exposure measurement error in air pollution epidemiology, *Air Quality, Atmosphere & Health*, 2011, Jun;5(2):203-216.

2. Szpiro AA, Paciorek C, Sheppard L. Does more accurate exposure prediction necessarily improve health effect estimates? *Epidemiology*, 2011b, 22:680-685.

3. Szpiro AA, Sheppard L, Lumley T. Efficient measurement error correction with spatially misaligned data. *Biostatistics*, 2011a, 12:610-23.

Posters

1. Keller JP, Sheppard L, Szpiro AA, Sampson PD. Spatial Analysis of a Marker of Roadway Emission Aging. Clean Air Research Centers Annual Meeting. Boston, MA, June 2012.

2. Vedal S, Szpiro AA. Methods for Estimating Health Effects of Multipollutant Mixtures in Cohort Studies. ISEE Annual Meeting. Barcelona, Spain, September 2011.

Presentations

1. Szpiro AA. Exposure Model Selection in Air Pollution Epidemiology: Single and Multiple Pollutants. Clean Air Research Centers Annual Meeting. Boston, MA, June 2012.

At the Clean Air Research Centers Annual meeting, and again at University of Washington, student Josh Keller presented a poster entitled "Characterization of pollutant aging by predicting the NO2/NOx ratio in the Multi-ethnic Study of Atherosclerosis and Air Pollution". This work combines Project 1 objectives with those of the MESA Air study.

Our goal was to use a simple characterization of some aspect of the pollutant aging process and to assess the presence of a spatial gradient for this simplified characterization. We chose the NO2/NOx ratio as we had direct measures of both (at the two-week time scale) and this ratio represents some aspects of the oxidation of NO into NO2, one reaction in the pollution aging process. We analyzed three existing two-week "snapshot" monitoring campaigns with approximately 100 samples each to begin to determine whether there is coherent spatial structure in the NO2/NOx ratio. We found fairly good structure in two seasons (summer and spring, with cross-validated R2 estimates of .58 and .56, respectively). The selected covariates and the predicted spatial fields varied somewhat between seasons. The results were weaker in the winter season (CV R2=.37). Overall we found our models for the ratio had weaker spatial structure our models for either pollutant alone.
We are currently undertaking additional exploratory analyses with the aim of developing spatial models to capture univariate summaries of multipollutant mixtures for epidemiological studies that use data that can feasibly be collected in epidemiological cohort studies.

At the Joint Statistical meetings in San Diego and at the Clean Air Research Centers Biostatistics Workshop, Adam Spiro presented talks on measurement error. His JSM talk title is "Exposure model selection in air pollution epidemiology: single and multiple pollutants". See the description of multipollutant health effects above for details of this work.

Future Activities

We have successfully recruited a postdoctoral fellow, Roman Jandarov, to support our methodological research program. With this enhanced staffing, we expect to make good progress in the next year on methods to quantify the health effects of multipollutant mixtures in a cohort study. We will focus on exposure prediction models, relying to the degree possible on the foundation provided by our currently developed spatio-temporal model. We will assess whether the multipollutant data we will be using will be rich enough to support this model or whether alternative approaches will be necessary.

We will continue Core activities to support all projects on an as needed basis. In the next year we expect the bulk of our effort will continue to support Project 1 investigators and staff with their data management and analysis.

Supplemental Keywords

Environmental Policy, Exposure Modeling, Epidemiologic Inference, Health Effects, Air Pollution Exposure

Project 1

Individual Project Title: Exposure Mapping – Characterization of Gases and Particles for Exposure Assessment in Health Effects and Laboratory Studies

Investigator	Institution
Michael Yost (PI)	University of Washington
Timothy Larson	University of Washington
Christopher Simpson	University of Washington
Thomas Jobson	Washington State University
Timothy VanReken	Washington State University

Objective of Research

Roadway-source air pollutants encompass a diversity of chemicals, including both particulate and gas phase components which are transformed by chemical and physical reactions as they age in the environment. Consequently, human exposures to air pollutants can range from relatively un-aged to highly aged components that vary with respect to particle size and the chemical composition of particle and gas phase components. To obtain a more comprehensive understanding of the seasonal and spatial variability in the concentration and composition of air pollutant exposures within MESA-Air cities, we employ mobile and fixed site monitoring to assess both gas and particle components of these pollutants as they age from roadway sources to population areas.

The main project objectives are:

1. Characterize spatial and temporal gradients of selected air pollutants along roadways and within neighborhoods in MESA cities using a mobile platform.

2. Measure spatial variation in concentrations of selected air pollutants at two-week average stationary sites in coordination with the mobile measurements.

3. Characterize aging of air pollutant components as they are transported from roadway sources to neighborhood receptor locations.

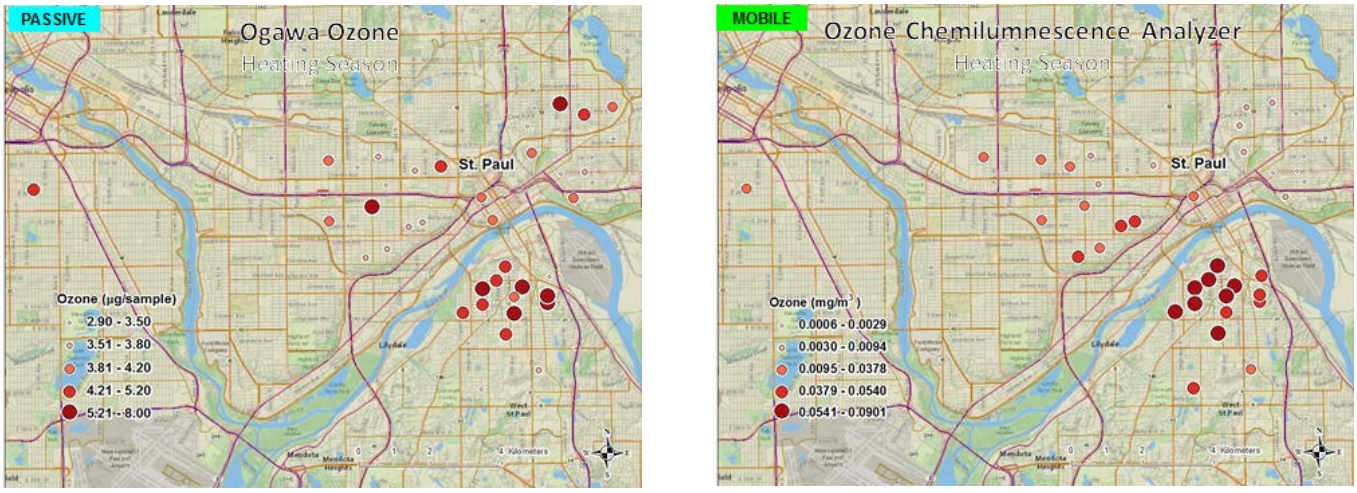
4. Provide detailed characterization of laboratory exposure conditions available for toxicology testing, and identify likely conditions that mimic those found in urban settings.

Progress Summary / Accomplishments

Aims 1 and 2 continue as the main focus of activities in this year 2 time period. This phase of the study is conducting field sampling through 2013 across 4 cities in the MESA-Air cohort: Minneapolis/St. Paul, MN, Baltimore, MD, Los Angeles, CA and Winston-Salem, NC. The instrument platform for mobile monitoring was assembled and tested in Seattle in October of 2011. Heating season measurements have been completed in Minneapolis/St. Paul and Baltimore; non-heating season measurements are completed in Baltimore and are underway in St. Paul. During each 2-week sampling period the mobile monitoring platform measures concentrations of particles and gases while continuously on the move along a fixed sampling route with position information simultaneously logged by a real time GPS. Data collection includes the following components: optical particle size in 31 size bins from 10 to 0.2um, particle mean diameter and particle count from 0.03 to 0.2um, total particle count >0.1um, particle light scattering coefficient, particle light absorption (black carbon), NO/NO_2, O_3, CO, CO_2 and total VOCs.

Pre-planned driving routes are created for each city, arranged into 3 sectors with 14 measurement intersection waypoints in each sector for measurement, plus a common central reference site. These 43 waypoints are selected in advance, based on a set of route criteria developed in consultation with the Biostatistics Core of the center. The routes are evaluated by the Biostatistics Core for use in the spatial mapping of exposures later in the study. These same waypoints coincide with placement of passive sampling devices deployed at the same time as the mobile monitoring. Figure 1 below illustrates the data collected from the winter sampling campaign in St Paul.

Figure 1 – Ozone Data Collected During Heating Season St. Paul, MN



Quintiles of Ozone data collected at 43 locations over the heating season in Minneapolis/St.Paul from mobile monitoring and passive sampling. The data represent the average at each location over the 2-week sample period. Reasonable agreement is found between the two types of measurements. Note the mobile data only is collected during the evening commute, while the passive badges collect continuously over the 2-week period.

In pursuance of Objective 4, detailed chemical characterization measurements were made of controlled exposure atmospheres at LRRI in May 2012. Over the course of three weeks, nearly 50 distinct exposure atmospheres were sampled. The majority of these test atmospheres were composed of unaged gasoline and diesel exhaust at various loadings and degrees of mixing; a few atmospheres were also sampled where the emissions were photochemically aged prior to sampling. All test atmospheres were sampled by the same instrument platform used for the mobile sampling. Additionally, the WSU collaborators sampled the test atmospheres with a high resolution time-of-flight aerosol mass spectrometer (HR-AMS) and a proton transfer reaction mass spectrometer (PTR-MS). The PTR-MS was coupled with a thermal desorption system for analyzing organic compounds with intermediate volatility. The HR-AMS and PTR-MS provided a much more detailed characterization of the particle- and gas-phase organic composition of the test atmospheres, which will yield improved understanding of the chemical characteristics and phase partitioning behavior of exhaust mixtures. Preliminary results from the experiments at LRRI were presented at the CLARC annual meeting. Detailed analysis is ongoing and multiple publications and presentations are expected in the coming year.

Relatively few problems have been encountered to date that have required any modifications in the project aims. After consulting with the Biostatistical Core, we determined that more passive samplers were needed to provide an adequate description of spatial variability in pollutants, and to reflect study subject residence concentrations. The main change has been to expand the number of passive samplers from 20 to 43 in each city. A standardized vehicle platform also was needed to improve logistics of the field sampling and to improve data QC. We attempted to use a hybrid vehicle to enable a more accurate measurement of roadway pollutants in traffic. However, this was not possible because most rental companies either don't offer a hybrid or have very few available. The same make/model vehicle (Ford Escape) is rented in each city during the measurement sessions.

Because of funding limitations associated with MESA Air and Project 5, epigenetic analyses are only available from a subset of the originally proposed MESA Air cities (See Project 5 Summary). As a result, both Project 5 and Project 1 altered their sample design to conduct air monitoring in the current four cities: St. Paul, Baltimore, Winston-Salem, and Los Angeles, while dropping New York and Chicago. This change, although not ideal with respect to epigenetics, does provide opportunities for monitoring increased pollutant concentrations in Los Angeles and more comprehensive participant health measurement.

Publications / Presentations / Posters

Posters

1. VanReken T, Jobson T. Chemical Characterization of the LRRI Exhaust Exposure Chambers by PTR-MS and HR-ToF-AMS: Early Results. Clean Air Research Centers Annual Meeting. Boston, MA, June 2012.

Future Activities

Activities in the next year will focus on completing the field sampling campaigns and assembling the data set for further analysis. We have completed most of the field work for the current year and are on

target to complete half of the field sampling by fall of 2012. Additionally, we scheduled field work for Los Angeles and Winston Salem and established the mobile monitoring routes for these cities. We also have scheduled the chamber characterization studies in Seattle/UW for next year. Data cleaning and QC review are underway for the cities that already have been sampled, and we are working with the Biostatistics core to automate the data QC process. Work on publications and dissemination of results for the first year of measurements will follow soon after the data set is ready. We anticipate starting the second year of field measurements in January and continuing over the next year, which will be similar to field deployments this past year.

Supplemental Keywords

Exposure science, Community Exposures, Chemical Transport, Mobile Monitoring

Project 2

Individual Project Title: Simulated Roadway Exposure Atmospheres for Laboratory Animal and Human Studies

Investigator	Institution
Jacob McDonald (PI)	Lovelace Respiratory Research Institute
Amie Lund	Lovelace Respiratory Research Institute

Objective of Research

Objectives/Hypothesis: Traffic-related emissions are associated with the incidence and progression of acute and chronic cardiovascular sequelae in human population studies; however, the causal components, subsequent chemical transformation of these components, and their associated toxicity on the cardiovascular system have not yet been determined. Project #2 is in progress to develop atmospheres with the primary objective of simulating environments containing key components of roadway emissions and the products of environmental factors that transform them. Previous, current, and future exposures are designed to determine air contaminants (or components) that cause or potentiate the toxicity of roadway emissions or confound interpretations based on roadway proximity alone.

Approach

This project will generate and characterize multiple complex roadway mixtures for subsequent animal and human exposure-related toxicology studies. In **Aim 1**, we will develop and characterize laboratory-generated exposure atmospheres simulating the key components of near-roadway exposures, including transformed emissions and co-exposures. **In Aim 2**, we will conduct inhalation exposures of laboratory animals (as described in Project 3). Lastly, **in Aim 3**, we will conduct inhalation exposures of human subjects in an effort to compare significant pathophysiological findings from our animal model exposures to responses in humans.

Expected Results

Results from these studies will identify key components, as well as the most potent combinations, of urban roadway and background copollutants that result in toxicological responses in the cardiovascular system of both rodents and humans.

Progress Summary / Accomplishments

Atmosphere development and characterization activities included the development of test atmospheres that further characterized the gas:particle partitioning and atmospheric processing. The motivation for this work was driven by guidance from the Scientific Advisory Committee, which wanted us to further investigate previous findings of enhanced vascular response after exposure to the mixture of gasoline and diesel exhaust. The hypothesis is that the combination of particle enriched and highly sorptive diesel exhaust with the vapor hydrocarbons and inorganics enhanced the toxicity, perhaps through increase in the delivered dose of materials to the deep lung. Several atmospheres and atmospheric characterization experiments were conducted to better elucidate these findings. In addition, atmospheric development was conducted on combinations on several of the important urban gas mixtures. Finally, atmosphere development was conducted to characterize and identify proper conditions for studies of the atmospheric transformation of motor vehicle emissions on toxicity.

Investigators from Project 1 visited LRRI and spent one month conducting detailed atmospheric measurements of motor vehicle emissions and irradiation chamber atmospheres. The aims of these characterizations are to bridge the laboratory atmosphere data to what is observed in the field sampling campaigns. During this work several sets of experiments were conducted and are under way to better define the role of gas/particle partitioning in the laboratory. A matrix of the experiments that were conducted is defined in Table 1 below, along with a representative figure (Figure 1) of the particle number counts and a picture of the investigators (Figure 2). The measurements in each of the test atmospheres included particle mass, particle number, volatile hydrocarbons, nitrogen oxides, ozone, carbon monoxide, carbon dioxide, and speciated volatile and semi-volatile hydrocarbons by mass spectrometry. Data integration and analysis of these atmospheres are under way.

LRRI Studies: Experimental Design

	Morning Run			Afternoon Run			Engine Load	
Experimental Target	PM ug/m3	PM ug/m3	PM ug/m3	PM ug/m3	PM ug/m3	PM ug/m3	DE Load	Gas Load
set-up	Chamber #4	Chamber #5	Chamber #6	Chamber #4	Chamber #5	Chamber #6		
Gas or diesel only Dilution (Hi, Lo)	180/UW, PTR	57/UW		43/UW, PTR			TYP	TYP
Gas 10% Diesel 90%	292 /UW, PTR	130 /PTR	334+12g UW PTR				TYP	TYP
Gas 90% Diesel 10%	30/All	50+23g/ALL	1+3g/All	19/UW	8/ALL		TYP	TYP
Gas & diesel 50:50 mix Dilution (Hi, Lo)	20/All	16+16g/All	222+22g/All	15/UW	34/All		TYP	TYP
Gas or Diesel Load+ Dilution (Hi, Lo)	42/UW,PTR	288/All	504+34g/All	17/UW		16+45g/All	High	Low
Gas or Diesel Load+ Dilution (Hi, Lo)	26/UW	72/All	114+4g/All		374/UW	304+33g/All	Low	High
Gas & Diesel 50:50 mix Dilution (Hi, Lo)	27/UW	52+34g/All	194+42g/All	11/All	372+35g/All	265/UW	High	High
Gas 90% Diesel 10%	9/UW	40+45g/All	8+9g/All	45	360+5g/All	200/UW	High	High
Cycle runs (Animal Expo Study Settings		Cycle Gas /All	DE & Gas Animal Mix				Typ	Var
COLOR KEY	DIESEL	GAS	MIXTURE	Sampled by UW, WSU (PTR, AMS) ALL				

Table 1 – LRRI Chamber Experiment Matrix

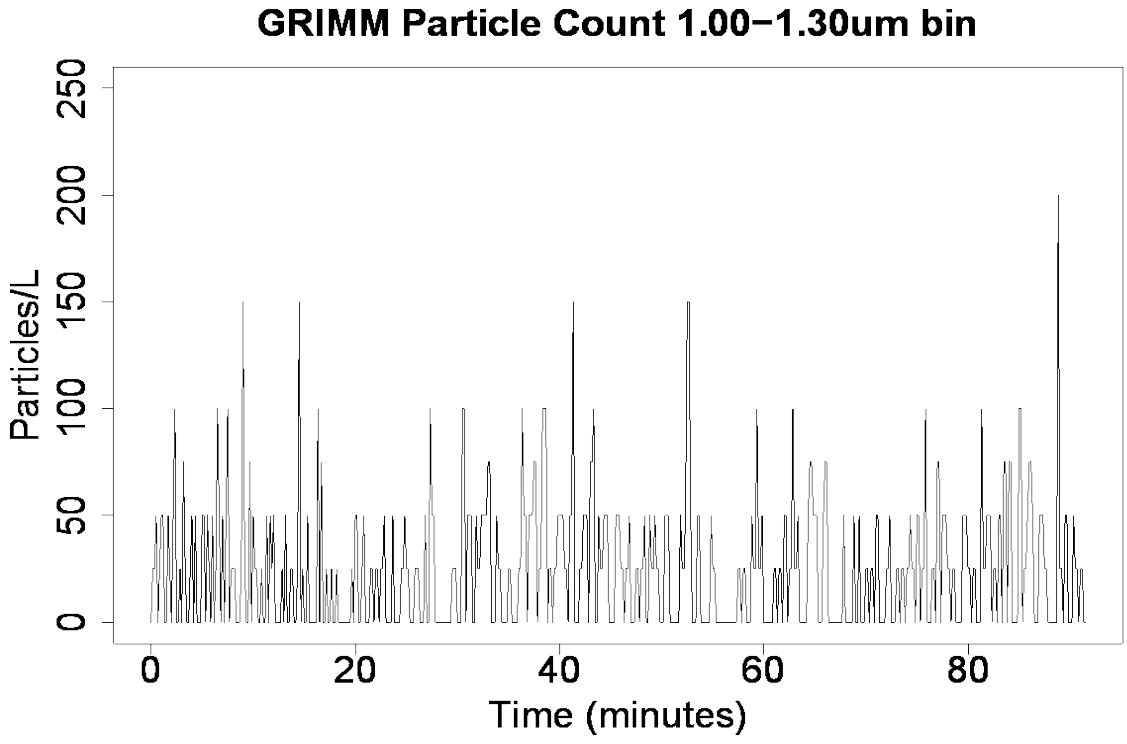


Figure 1 - Grimm instrument particle count concentration during test atmosphere characterization for high concentration of high load diesel exhaust.

Figure 2 - Picture of UW/WSU/LRRI team conducting characterizations of toxicology chamber atmospheres.

In addition to the studies defined above, further atmosphere development focused on creating atmospheres that would allow us to investigate test atmospheres that 'tease' out the role of gases versus particles in novel ways, and that further evaluate the role of physical aging of motor vehicle exhaust. Studies currently under way include atmospheres to evaluate;

- Mixed motor vehicle exhaust
- Mixed motor vehicle exhaust minus particles
- Mixed motor vehicle exhaust minus gases (includes particles)
- Mixed motor vehicle exhaust minus NOx and ultrafines (simulates downwind)

These atmospheres were developed to address key CCAR questions related to transformation and multipolltant components that are most important for toxicity. To develop atmospheres minus particles, HEPA filters are used. The atmospheres remove 99 % of the particles and permit the gases to pass through. The atmosphere with the gases removed was developed with the use of the HARVARD parallel plate denuder. The denuder was loaned to CCAR from the Harvard CLARC. This denuder allows the removal of 95% of all gases with only small (<5%) particle loss, mostly in the ultrafine range. A fourth condition uses the DRI cobalt oxide denuder (see below) to remove NOx and ultrafine particles. The NOx denuder removes 95 % of the NOx and allows other gases to pass through. It also removes the smallest fraction of particles that may agglomerate and be removed in close proximity to roadways. Figures 3 and 4 illustrate the change in particle size resulting from the denuder.

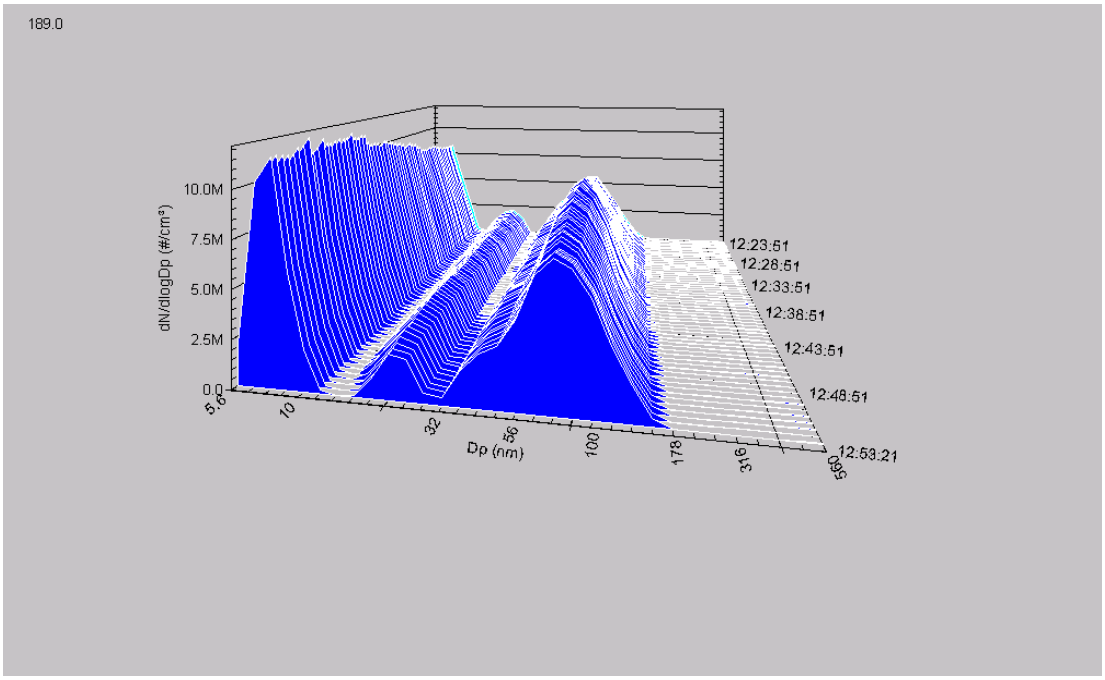


Figure 3 - Particle size distribution for mixed engine exhaust (MEE) atmosphere

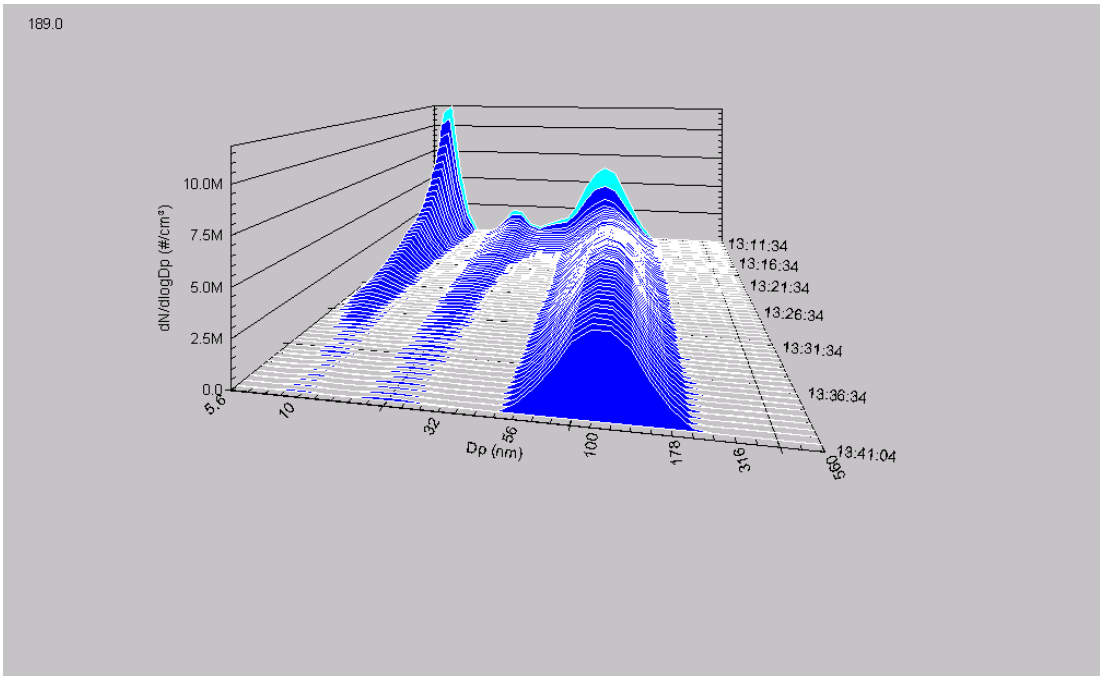


Figure 4 - Particle size distribution for mixed engine exhaust atmosphere **with denuder.**

As proposed in Aim 1, over the past year we have conducted two sets of exposures and have a third exposure currently in progress. The purposes of the first two rounds of exposures were to characterize the appropriate animal model, duration, and concentration for subsequent exposures. Two separate 7-day exposures to mixed vehicular emissions (MVE; combined gasoline and diesel engine emission) were executed to ascertain our ability to discriminate vascular toxicity (oxidative stress, inflammation, toxicity) in our study permutations proposed in Aim 1 of Project 3. $ApoE^{-/-}$ and $LDLR^{-/-}$ mouse models, on a high fat or normal chow diet, were exposed to two different concentrations of MVE. In the first set of exposures, animals were exposed via whole-body inhalation to: 100 μg PM/m^3 MVE, which was comprised of 30 μg PM/m^3 derived from a gasoline engine combined with 70 μg PM/m^3 derived from a diesel engine. In the second set of exposures, animals were exposed to: 300 μg PM/m^3 MVE, which was comprised of 30 μg PM/m^3 derived from a gasoline engine combined with 270 μg PM/m^3 derived from a diesel engine. Resulting exposure-mediated toxicity was then analyzed through assays that include lipid peroxidation, dihydroethidium staining (to detect reactive oxygen species), nitrotyrosine staining (to detect peroxynitrite), and quantification of macrophage/monocyte (MOMA-2) infiltration in the vasculature of study animals, as described in Project 3. Briefly, more consistent results in vascular toxicity endpoints were observed in the mice exposed at the 300 μg PM/m^3 concentration; however it was determined that a longer exposure duration was needed in order to obtain statistically significant alterations in expression of these endpoints between exposures groups.

Based on the results obtained under Project 3, we are now in the process of beginning a 50-day exposure of Apo E -/- mice , on a high fat diet, to the following chemistries: (1) MVE, 300 μg PM/m^3: 30 μg PM/m^3 derived from a gasoline engine combined with 270 μg PM/m^3 derived from a diesel engine; (2) MVE at the 300 μg PM/m^3 concentration with PM filtered; (3) MVE at the 300 μg PM/m^3 concentration with gases filtered, using a denuder; (4) MVE at the 300 μg PM/m^3 concentration with NOx scrubbed out; and (5) filtered air (controls). At the completion of exposures (August, 2012), resulting alterations in lipid profiles and markers of vascular toxicity will be assessed in an effort to differentiate effects of co-pollutants on the cardiovascular system.

Publications / Presentations / Posters

There have been no Project 2 presentations, publications, or posters to date.

Future Activities

The longer duration studies under way are investigating the gas;particle partitioning and impact of NOx on vascular toxicity. The next round of studies will include the atmospheric reaction chamber and urban background studies.

Supplemental Keywords

Inhalation toxicology, diesel, gasoline engine

Project 3

Individual Project Title: Cardiovascular Consequences of Immune Modification by Traffic-Related Emissions

Investigator	Institution
Matthew Campen (Co-PI)	University of New Mexico
Michael Rosenfeld (Co-PI)	University of Washington
Jacob McDonald	Lovelace Respiratory Research Institute
Amie Lund	Lovelace Respiratory Research Institute

Objective of Research

Objectives/Hypothesis: Traffic-related emissions are associated with the incidence and progression of acute and chronic cardiovascular sequelae in human population studies. Such phenomena of near-roadway health effects have yet to be characterized toxicologically. Because of overlapping issues related to noise, socioeconomic status, ethnicity, etc, there is a need to better understand the biological plausibility that fresh mixtures of vehicular emissions have a more potent than expected impact on human health. We hypothesize that the complex mixtures produced by traffic are inherently more toxic due to the combined presence of both particulates and volatile organic emissions. Furthermore, we hypothesize that emissions-induced oxidation of certain endogenous phospholipids, presumably from the pulmonary surfactant, can stimulate the activity of immune cells through such receptors and in turn promote the invasion of existing vascular lesions.

Approach

This project will use complex roadway mixtures as generated and characterized in the laboratory.

Aim 1 - We will ascertain 1) the potentiating effects of physical and photochemical aging on fresh emissions and 2) interactions of vehicular emissions with pertinent copollutants (ozone, road dust), both in terms of driving systemic vascular oxidative stress**.**

Aim 2 - We will examine effects of the emissions-induced oxidative modifications to endogenous phospholipids, in terms of activating immune-modulating receptors such as LOX-1, CD-36, TLR-2, and TLR-4. This Aim will utilize transgenic models to examine the roles of these receptors, as well as characterize the lipidomic alterations in various tissues.

Aim 3 - We will further explore the role of specific immune cell populations as participants in the innate and adaptive responses to emissions-induced phospholipid modifications. In this Aim, we will utilize mouse models of immunodeficiency, including SCID and B-Cell deficient models. Additionally, we will pursue bone-marrow transplants from mice lacking those receptors described in Aim 2 to mechanistically establish the involvement of the oxidatively-modified phospholipids.

Expected Results

Findings will:

1) Indicate the most potent combinations of urban roadway and background co-pollutants in terms of vascular toxicity.

2) Detail the role of the immune system in mechanistically driving the systemic effects of inhaled pollutants.

Progress Summary / Accomplishments

First, we conducted 2 x 7-day exposures to MVE to ascertain our ability to discriminate vascular toxicity (oxidative stress, inflammation, toxicity) in our study permutations proposed in Aim 1. We compared between $ApoE^{-/-}$ and $LDLR^{-/-}$ mouse models on a high fat or normal chow diet at exposure levels of 100 and 300 μg PM/m^3. Additionally, we compared lipid peroxidation in vascular wall compared to perivascular fat. While our outcomes were more varied than we had previously observed (Lund et al.,2011), we felt confident that the most potent responses to mixed vehicular emissions (diesel + gasoline emissions) were in the perivascular fat of mice fed the high fat diet. It was not clear that the strain of mouse had a significant impact on the outcome, although the relative magnitude of effect was greater in $LDLR^{-/-}$ compared to $ApoE^{-/-}$ mice. While the outcome of this pilot work is of limited external value, it does go a long way towards helping us make decisions for future exposures, as was the plan for this Aim.

Upon sharing these data with the Scientific Advisory Committee, it was recommended that we explore several more sensitive and diverse markers of cellular redox stress. We have expanded our endpoints to include dihydroethidium staining (indicative of reactive oxygen species) and 3-nitrotyrosine staining (indicative of peroxynitrite formation).

Additionally, we have explored advanced in vivo imaging techniques to facilitate longitudinal assessment for changes in vascular and pulmonary inflammation and also cardiac function. To assess inflammation, a ligand to the leukocyte-function antigen (LFA-1) is linked to ^{111}Indium via an Norbirt intermediate. This imaging construct is intravenously delivered and decays are detected by a small animal SPECT/CT system. Reconstruction of decays is linked to the CT image to provide anatomical reference. In a short pilot study, $ApoE^{-/-}$ mice were placed on a high fat chow for 2 weeks, then exposed to a week of 0.8 ppm O_3 for 4h/d. Imaging revealed a consistent increase in cardiac and thoracic inflammation, likely as a result of the high fat diet, while ozone exposure induced a significant shift in rate of LFA-1 staining for both lungs and heart.

Simultaneously, we can image cardiac function by either ^{201}Thallium or ^{99}Tc-Sestamibi, which provide information on coronary flow/perfusion and, when paired with the timing information from an ECG record, allows function output of systolic and diastolic left ventricular volumes.

Combined, these new assays will provide a greater profile of toxicity and inflammation induced by the varied atmospheres proposed for Aims 1 and 2. We will be able to apply these to the exposures currently underway.

Publications / Presentations / Posters

Publications

1. Campen MJ, Lund A, Rosenfeld M. Mechanisms linking traffic-related air pollution and atherosclerosis. Curr Opin Pulm Med. 2012 Mar;18(2):155-60. PMID: 22189455

Posters

1. Campen MJ, McDonald JM, Rosenfeld ME, Lund AK. Cardiovascular Consequences of Immune Modification by Traffic-Related Emissions. Clean Air Research Centers Annual Meeting. Boston, MA, June 2012.

Future Activities

Aim 1: With 50d exposures, continue a characterization of cardiovascular toxicity of the varied mixtures of gasoline and diesel emissions at different ratios.

Aim 2: Place double knockout models into exposures beginning late fall 2012. We anticipate an initial study with $ApoE^{-/-}xTLR4^{-/-}$ as our first undertaking, followed by $ApoE^{-/-}xCD36^{-/-}$.

Aim 3: The development of chimeric mice will wait until the end of the coming annual cycle, enabling exposures in year 4.

Supplemental Keywords

Coronary Artery Disease, Oxidized Phospholipids, Atherosclerosis, Particulate Matter, Volatile Organic Compounds, Carbon Monoxide, Ozone

Project 4

Individual Project Title: Vascular Response to Traffic-Derived Inhalation in Humans

Investigator	Institution
Joel Kaufman (PI)	University of Washington
Jacob McDonald	Lovelace Respiratory Research Institute
Amie Lund	Lovelace Respiratory Research Institute

Objective of Research

Project 4 examines the acute vascular effects of model traffic-derived inhalation exposures in human subjects, in a multi-pollutant context. The project uses controlled clinical exposures to examine specific hypotheses based on the premise that traffic-related air pollutants acutely trigger increased arterial reactivity, vasoconstriction, and increased blood pressure in humans, and that these responses will vary depending on the components and sources of those exposures. We will test the hypothesis that traffic (e.g., diesel and gasoline engine) –derived aerosols exert vascular effects in human subjects, and provide insight into the most toxic components and mechanisms underlying epidemiological observations of cardiovascular disease events and mortality.

Progress Summary / Accomplishments

Project 4 is planned to begin human studies in Year 3 of the Center. The experiments will be customized based on findings in Center Projects 1-3.

Building on data derived from animal studies and exposure characterization studies in Center years 1 and 2, and by customizing exposures to capitalize on those findings, we plan clinical experiments nested within a crossover trial to be primarily conducted in Center years 3 and 4. In healthy subjects, we will test whether a traffic-derived laboratory-generated high-potency pollution atmosphere, as suggested through other Center projects, causes an increased vascular response (brachial artery vasoconstriction and increased blood pressure) compared with both a roadway-derived exposure of hypothesized lower potency, and with filtered air. Our External Scientific Advisory Committee suggested that we simplify our Project 4 protocol, and we are taking that suggestion seriously.

Projects funded from other sources are ongoing in the human exposure facility, and we anticipate no new obstacles to completing the proposed Center-funded work. We are currently conducting a different experimental protocol, with exposure to diesel exhaust, which we plan to have completed by Center Year 3. This protocol will permit us to conduct pilot evaluations of the proposed procedures to be used in Center Project 4, as we ramp up Center activities in the laboratory in anticipation of the launch of the Center-funded protocol in Year 3.

The new experimental protocol (supported primarily by NIEHS 5P50ES015915) being launched has received IRB approval without controversy, and we do not anticipate difficulties with approval for the Center-funded activities that will follow this protocol. We modified our consent process slightly to

reflect the International Agency for Research on Cancer determination that diesel exhaust emissions represented a human carcinogen. We briefly suspended our exposures while awaiting approval of the new language. Our IRB approved the modification, and participants are being recruited and exposed again using the revised materials. We anticipate moving forward with IRB approval for the CCAR Project 4 protocol shortly, so that it is ready to proceed in Center year 3.

Publications / Presentations / Posters

Publications

1. Cosselman KE, Krishnan RM, Oron AP, Jansen K, Peretz A, Sullivan JH, Larson TV, Kaufman JD. Blood Pressure Response to Controlled Diesel Exhaust Exposure in Human Subjects. Hypertension. 2012 May;59(5):943-8. Epub 2012 Mar 19. PMID: 22431582

Future Activities

During Year 3 of this project, we will launch the Center-sponsored experimental protocol on time and with all procedures adequately pilot-tested.

Supplemental Keywords

Cardiovascular Health, Diesel Exhaust, Gasoline Exhaust, Fine Particles, Volatile Organic Compounds, Blood Pressure

Project 5

Individual Project Title: Effects of long-term exposure to traffic-derived aerosols and gases on subclinical measures of cardiovascular disease and DNA methylation in a multi-ethnic cohort

Investigator	Institution
Joel Kaufman (PI)	University of Washington
Sverre Vedal	University of Washington
Timothy Larson	University of Washington
Michael Yost	University of Washington
Elizabeth A. (Lianne) Sheppard	University of Washington
Paul Sampson	University of Washington
Adam Szpiro	University of Washington

Objective of Research

Project 5 has three primary objectives:

1. Employ the small-scale gradient data acquired as part of the mobile monitoring campaign in Project 1, in conjunction with central fixed site data, regulatory monitoring data, and geographic covariates, to build a multi-pollutant exposure model for traffic-derived air pollutants. This model will incorporate complex spatial information on primary and secondary traffic-derived particles and gases.

2. Develop and validate individual-level exposure estimates for traffic-derived air pollutants, integrating: i) the outdoor residential concentration estimates from the multi-pollutant model; ii) estimates of residential infiltration rates; iii) road class- and traffic condition-specific estimates of on-roadway concentrations; and iv) individual-level questionnaire-derived time-location information. These individual-level exposure estimates will also utilize personal monitoring data designed to clarify the in-transit component of total exposure.

3. Estimate the effect of individual-level exposure to traffic-derived air pollution on subclinical cardiovascular disease using these exposure models. Health outcomes will include left ventricular myocardial mass as ascertained by MRI, arteriolar diameters as measured by retinal photography, coronary artery calcium as ascertained by CT, intima-medial thickness as measured by ultrasound, and DNA methylation.

Progress Summary / Accomplishments

Over the past year, a significant amount of planning has gone into Project 5. Project initiation has been delayed by the extension of MESA Exam 5. This exam has recently concluded, and we have now been able to begin to coordinate the field work portion of this project with the participating field centers at Wake Forest University and UCLA. The current plan is for these field activities to begin in January of 2013 in Winston Salem, followed quickly by a February sampling event in Los Angeles.

In each city, we will be visiting the residences of approximately 40 participants, and deploying indoor, outdoor, personal, and in-vehicle monitors at each location. We will also be providing each participant with a GPS data-logger to wear consistently throughout the 2 week sampling period, and will be asking them to complete time-location diaries. Based on the logistics inherent in this effort, we will be sending two teams of two technicians out for each sampling event (twice what we had originally proposed). We expect that these teams can each visit three homes per day.

The ideal situation would be for the sampling included in this project to overlap exactly with the two-week sampling event occurring in Project 1. However, since we can only sample 6 homes per day, we will need to allow there to be a date mismatch of up to 3 days in either direction. Therefore, we will deploy samplers every day for a 7 day period, centered on the beginning of the Project 1 sampling. Therefore, while we had originally planned to include 72 participants per sampling event, we now plan to include 42 (6 per day for 7 days).

In addition to developing our plan to integrate with Project 1, we also have been working to develop our GPS data logger, which has been pilot tested by several staff members. This device has been developed to have sufficient battery life to track a participant for a full two weeks without requiring charging, and we are currently evaluating its spatial accuracy. In addition, we have been working to develop the technology for our in-vehicle sampling, as well as proximity monitors to allow identification of specifically when each participant is inside their homes or in their cars. We have also been developing the survey instruments we will use to collect self-reported time-location information.

Publications / Presentations / Posters

Presentations

1. Vedal S, Szpiro AA. Methods for Estimating Health Effects of Multipollutant Mixtures in Cohort Studies. ISEE Annual Meeting. Barcelona, Spain, September 2011.

Future Activities

The next phase of this project will be to work with the field centers at Wake Forest University and UCLA to create subcontracts for the portion of this work that will employ field center staff, including participant recruitment and consent. These subcontracts are expected in Project Year 3. Once those subcontracts have been established, we will work with the field centers to submit materials to their Internal Review Boards for Human Subject approvals.

We will also be submitting a modification to add this work as an ancillary study to the already approved Human Subjects application (#26962). Currently, we anticipate including participants with the following characteristics: 1) previously consented to be contacted regarding personal and residential monitoring as part of MESA Air; 2) own and drive their own car as a primary mode of transportation; 3) intend to be spending their time primarily at their primary residence during the sampling period; 4) and are non-smokers. We intend to recruit participants specifically to represent those who report a range of time spent in transit, road types traveled, and traffic conditions experienced, based on their responses to the MESA Air questionnaires that they completed previously.

Supplemental Keywords

Cardiovascular Disease, Subclinical

CLARC Program Collaborations

We are committed to participating in four of the five CLARC collaborative projects that have been proposed. The individual projects, the investigators from the CCAR team and approximate time periods and total budgets are included in the table below.

UW CCAR Involvement in the CLARC Collaborative Projects				
PROJECTS	**CCAR Investigators**	**Activities**	**Period**	**Estimated total budget**
Animal Toxicology	Matt Campen Jake McDonald	• Ex Vivo Endothelial Cell Assays • High Fructose Rat Model in Designed Exposure Atmospheres	10/12-11/13	TBD
Mobile and Fixed Site Characterization	Tim Larson Mike Yost	• Mobile and Fixed Site Monitoring Campaign in Atlanta	10/12-11/13	TBD
Measurement Error	Adam Szpiro	• Measurement Error Correction Approach to Georgia Birth Cohort	12/12-11/14	TBD
Satellite PM2.5 Estimation	Paul Sampson	• Satellite PM Metric Addition to the PM Spatio-Temporal Model in North Carolina	12/12-11/13	TBD
Chamber chemical Characterization				