University of Washington Center for Clean Air Research (UW CCAR)

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Director: Sverre Vedal
University of Washington, Seattle, WA

EPA Grant Number: R834796-01

Center Overview:

Objectives: The UW CCAR is focused on the cardiovascular health effects of near-roadway pollution, a complex mixture of particle, vapor and gas phase components that vary by vehicle emission source, road surface, extent of physical aging and the type and degree of atmospheric processing and photochemical reactions. This exposure scenario is not only known to be of considerable health importance, it also serves as a prototypical case for developing research approaches to dealing with multi-pollutant exposure-effect relationships. 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.

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

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

Project 1: Exposure Mapping – Characterization of Gases and Particles for Exposure Assessment in Health Effects and Laboratory Studies

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EPA Grant Number: R834796-01

Project Summary:

Objectives: 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. This proposal is will 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, for a more comprehensive understanding of the seasonal and spatial variability in the concentration and composition of air pollutant exposures within MESA-Air cities. 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 fixed sites in coordination with the mobile measurements. (3) Characterize aging of air pollutant components transported from roadway sources to neighborhood receptor locations; and (4) Provide detailed characterization of laboratory exposure conditions available for toxicology testing, and identify likely conditions that mimic those found in urban settings.

Approach: We will (1) use mobile monitoring with an instrument platform designed to measure concentrations of particles and gases while continuously on the move. These data will be used by the Biostatistics Core to develop multivariate spatial models of selected roadway-source air pollutants for use in health studies, and to characterize the aging of air pollutant components as they are transported from sources to populated areas; (2) use passive monitoring at approximately 20 stationary sites in each of the four MESA cities to measure concentrations of coarse particles, gases (O_3, SO_2, NO, NO_2), and selected volatile organic compounds (VOCs). These measurements will be used in conjunction with the mobile measurements to develop multivariate spatial models of selected roadway-source air pollutants; (3) characterize the laboratory exposure conditions available for toxicology testing, and identify likely conditions that mimic those found in urban settings. This will be achieved by deploying the same instruments used in the mobile monitoring platform, along with LRRI instruments and additional high sensitivity mass-spectrometer instruments only available for the laboratory facilities (Aerosol TOF-MS for particles and PTR-MS for VOCs).

Expected Results: In this project, we will (1) develop multivariate spatial models of selected roadway-source air pollutants for use in health studies; (2) characterize the aging of roadway source air pollutant components as they are transported from sources to populated areas; (3) characterize the laboratory multi-pollutant atmospheres for toxicology testing, to help describe physical and chemical transformation processes occurring in the laboratory and to help determine the comparability of conditions generated by in the laboratory to those observed in the field.

Project 2: Simulated Roadway Exposure Atmospheres for Laboratory Animal and Human Studies

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Co-PI: Joe L. Mauderly, Melanie Doyle-Eisele, Tim Larson
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EPA Grant Number: R834796-01

Project Summary:

Objectives: This Project will develop inhalation exposure atmospheres for animal and human laboratory studies, with the primary objective of simulating environments containing key components of roadway emissions and the products of environmental factors that transform them. The exposures will help determine air contaminants that cause or potentiate the toxicity of roadway emissions or confound interpretations based on roadway proximity alone. Our hypotheses are that combined gasoline and diesel motor vehicle emissions toxicity decreases when transformed in the atmosphere. We further hypothesize that background air and nonexhaust roadway emissions (road surface dust, tire and brake wear material, inorganic ions, metals, and ozone) do not contribute significantly to roadway-associated cardiovascular morbidity, nor do they potentiate the morbidity associated with roadway emissions. The animal and human toxicology projects will utilize the experimental exposure atmospheres generated in this project to determine the relative potency of different simulated roadway environments, and thus test hypotheses regarding causal components and combinations. The results of the animal studies will be used to select atmospheres for confirmatory human inhalation studies.

Approach: We will develop novel inhalation exposure atmospheres that simulate near roadway and downwind motor vehicle emissions after physical and chemical transformation in the air. Physical aging will be used to convert ultrafine particles that are emitted from the tailpipe at 10-20 nm to agglomerated particles that are 100-150 nm. A third atmosphere will utilize an irradiation chamber to chemically transform motor vehicle emissions. Non-tailpipe roadway emissions will be simulated by a road dust atmosphere with and without motor vehicle emissions. Urban background will be created to include a mixture on non-motor vehicle exhaust that includes ozone, hydrocarbons, metals and inorganic ions (sulfate/nitrate). Urban background potency will be compared against and in combination with motor vehicle emissions. We will define the biological potency of each atmosphere based on lipid peroxidation in ApoE-/-mice (further described in Project 3).

Expected Results: We will elucidate the important characteristics that define toxicity resulting from roadway emissions and their interaction with background air. We expect that fresh whole exhaust containing ultrafine particles and vapor will confer the most potent atmosphere. These results will be confirmed in both rodent and human studies.

Project 3: Cardiovascular Consequences of Immune Modification by Traffic-Related Emissions

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EPA Grant Number: R834796-01

Project Summary:

Objectives: 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. In **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. In **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. Lastly, in **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 copollutants in terms of vascular toxicity and 2) detail the role of the immune system in mechanistically driving the systemic effects of inhaled pollutants.

Project 4: Vascular Response to Traffic-Derived Inhalation in Humans

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EPA Grant Number: R834796-01

Project Summary:

Objectives: Air pollution exposures are associated with ischemic heart diseases. Recent observations demonstrate that traffic-related air pollutants acutely trigger increased arterial reactivity, vasoconstriction, and increased blood pressure in humans and animals; these effects can be used to understand both acute and chronic health effects of air pollutants. This project will use controlled clinical exposures to test the hypothesis that traffic-derived (e.g., diesel and gasoline engine) aerosols exert vascular effects in human subjects, and provide insight into the most toxic components and underlying mechanisms.

Approach: We will use a well-characterized human exposure facility, customized to reflect findings in Center Projects 1-3, to examine effects of simulated roadway-derived exhaust in a double-blind, randomized, controlled crossover experiment. Building on data derived from animal studies and exposure characterization studies (Projects 1-3) in Center years 1 and 2, we propose clinical experiments nested within a crossover trial to be largely 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. We also propose several nested aims to examine hypotheses in healthy volunteers in order to better understand the epidemiological observations of both acute (triggering) and chronic (pro-atherogenic) air pollution effects. These nested aims include: whether specific exhaust-related monocytic gene expression effects are mediated by lipid peroxidation and blocked by an anti-oxidant; whether traffic-related pollutants' vasoconstrictive effects are increased in subjects with a common SNP variant in the gene coding for lipoxygenase-15; and whether lymphocyte DNA hypermethylation in specific genes is increased with exposure to simulated roadway-derived exposures.

Expected Results: By coordinating closely with Center Projects 1-3, we will determine whether specific aspects of traffic-derived exposure (primary vs. secondary organics, particulate vs. gases, spark-ignition vs. diesel engine vs. a mixture) enhance the human vascular response to pollutants. We also will learn about biological mechanisms involved in human health effects from traffic pollutants. These studies will have important implications for air pollution regulatory efforts and suggest new approaches for the prevention of cardiovascular health effects.

Project 5: Effects of Long-term Exposure to Traffic-derived Particles and Gases on Subclinical Measures of Cardiovascular Disease in a Multi-ethnic Cohort

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EPA Grant Number: R834796-01

Project Summary:

Objectives: Exposure to air pollution, especially particulate matter (PM), is consistently linked to cardiovascular disease (CVD) in epidemiological studies. Larger effects of long-term PM exposure are seen with improved exposure estimates. Traffic is a major source of air pollution and an important contributor to CVD; integrating refined traffic exposures into an epidemiologic study of air pollution and CVD would be an important advance. The primary objective of this project is to estimate the effect of individual-level exposure to traffic-derived air pollution on measures of CVD in the Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air) using novel exposure estimation methods and incorporating on-road, in-transit exposure estimates.

Approach: This project has three tasks. First, a multi-pollutant exposure prediction model for roadway-associated air pollution will be built that incorporates complex spatial information on primary and secondary traffic-derived particles and gases. This model will yield: 1) city-wide exposure surfaces for traffic-derived air pollution components for four study cities, and 2) distributions of traffic-derived air pollutant estimates for various roadway types and traffic conditions in each city. Second, individual-level exposure estimates will be developed for traffic-derived air pollutants, utilizing the models built under the first objective. We will enhance and validate these estimates using a personal, residential, and in-vehicle monitoring campaign, including real-time data logged GPS tracking, in a subset of 144 MESA Air participants. Third, the effect of individual-level exposure to traffic-related air pollution, including on-roadway exposures, on longitudinal vascular outcomes (including left ventricular mass and retinal arteriolar diameter) and DNA methylation will be estimated in a cohort of over 4,000 MESA Air participants.

Expected Results: This project will transform MESA Air from its current focus on $PM_{2.5}$ into a multi-pollutant study that can meaningfully investigate the impact of traffic-derived air pollution on cardiovascular health using a source-to-exposure approach. We will integrate data on traffic-derived pollutants from the novel, state-of-the-art mobile monitoring campaign (Project 1) into a multi-pollutant exposure model that incorporates participant-specific time-location information. The relationship between traffic exposure and change in measures of CVD will be assessed in a large and well-characterized cohort, making this project the first application of a multi-pollutant approach to a large-scale air pollution epidemiology study. Results will, in turn, assist policymakers in taking a multi-pollutant approach to controlling adverse health impacts of air pollution exposure.