Harvard University
Clean Air Research Center

Air Pollution Mixtures: Health Effects across Life Stages

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EPA Grant Number: R834798-01

Center Overview:

Objectives: The main objectives of the proposed Center are: 1) to investigate the acute and chronic health effects across life stages of six exposure metrics (short- and long-term exposures to individual pollutants, pollution sources and multi-pollutant mixtures) on: cognitive/neuropsychological function, cardiovascular/endothelial function, inflammation, birth weight/growth, and CVD-related hospitalization/mortality; and 2) to identify susceptibility and vulnerability factors that modify these effects.

Approach: Project 1 will investigate the toxicity of air pollutant mixtures in Boston, focusing on the identification of pollutant characteristics that are responsible for the most toxic effects, including: individual components, combinations of components (mixtures), formation processes, and source types. Exposures will be generated using a novel integration of our ambient particle concentrator and photochemical chamber technologies. Sprague-Dawley rats will be exposed and toxicity will be assessed by changes in: in vivo oxidant response, blood pressure, inflammation, and vascular reactivity. Projects 2-5 will examine the health effects of the six exposure metrics on multiple integrated specific health outcomes. **Project 2** will examine effects of these exposure metrics on cognitive and neuropsychological function; cardiovascular and endothelial function; inflammation; and oxidative stress among elderly individuals living in New England enrolled in the Normative Aging Study. **Project 3** will investigate effects of the six metrics on cognitive impairment and interference, as well as vascular and endothelial function, among middle-aged and older adults living in New England enrolled in the Framingham Offspring and Third Generation Study. **Project 4** will investigate effects of the metrics on somatic growth, blood pressure, cardiovascular fitness, and cognition, in the Viva ongoing pre-birth study of over 1,300 children from Eastern Massachusetts. **Project 5** will estimate mortality and hospitalization risks in hundreds of Counties across the US. It will also study two cohorts in New England to: 1) estimate risks of adverse birth outcomes using approximately 700,000 live births; and 2) assess mortality and morbidity risks using 2.3 million Medicare enrollees. Finally, these Projects (2-5) will study the modifying effect of measures of susceptibility (clinical/biologic) and vulnerability (social milieu) and will link outcomes to the same pollution mixtures across all life stages.

Expected Results: Our Center will address four of the six research priorities of the EPA solicitation to establish Clean Air Centers. It will: 1) investigate the effects of pollutants and mixtures through animal and human studies; 2) identify sub-populations that are at increased risk through the investigation of the modifying effects of gender, diabetes, obesity, socioeconomic disparities, stress, depression, violence, smoking, and omega-3 fatty acid intake in children, adults, and elderly; 3) explain regional and temporal differences in air pollution risks; and 4) examine the shapes of exposure-response relationships for associations resulting from the use of multiple exposure metrics, outcomes and populations.

Project 1: Relative Toxicity of Air Pollution Mixtures

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EPA Grant Number: R834798-01

Project Summary:

Objectives: Project 1, an inhalation toxicological animal exposure study, will investigate the relative toxicity of different component concentration combinations of air pollution mixtures. These components include both particles and gases that are emitted directly from sources (primary species) or are formed in the atmosphere through a series of reactions that are predominantly photochemical (secondary species) Using a novel integration of our ambient particle concentrator and photochemical chamber technologies to generate realistic mixtures, we will test these specific hypotheses: (i) secondary gaseous pollutants formed from the photochemical oxidation of Boston ambient gases can induce biological responses; (ii) aging Boston concentrated ambient particles (CAPs) in the photochemical chamber enhances their toxicity; (iii) toxicological effects of photochemically aged CAPs are exacerbated by co-exposure to ozone and other secondary gases; and (iv) mixture composition and toxicity exhibit inter- and intra-seasonal variability due to changes in source emissions and weather conditions.

Approach: Toxicity will be assessed in Sprague-Dawley rats by changes in 1) in vivo oxidant response, 2) blood pressure, 3) measures of inflammation, and 4) vascular blood flow/resistance. Three concurrent exposures groups (Sham, Control Exposure and Exposure) will allow us to control for the variability in CAPs composition. With this design, there can always be a direct comparison between two exposure mixtures on every exposure day, making it possible to determine which mixture is more toxic. In studies of vascular blood flow/resistance using a crossover design, each animal will have multiple exposures that will include each of the three types, including baseline measurements. This will permit for control of inter-subject variability in the biological response. Exposure atmospheres will be chemically and physically characterized using a broad array of measurement techniques for CO, NOx, O_3, PM, BC, particle count and size distribution, EC/OC, elemental composition, sulfate, formaldehyde, acetaldehyde and VOCs. For the biological effects observed during each exposure, inter-group differences will be assessed using multi-way analysis of variance. To determine the effect of PM composition on biological response, linear regression models containing **exposure** concentrations as predictors will be fitted to each **response** outcome measure. Multiple pollutant linear regressions will be used to assess the independent effects of multiple pollution components on biological response.

Expected Results: The proposed study will differentiate the health effects of components of multi-pollutant exposure mixtures. We expect to add to our understanding of the exposure-response relationship, the interaction between particulate matter and photochemical gases, and the extent to which the resultant products exert toxicity. The biological outcomes assessed in this Project focus on responses important in oxidant initiation of pulmonary inflammation, and important functional measures of vascular and cardiovascular health.

Project 2: Cognitive Decline, Cardiovascular Changes, and Biological Aging in Response to Air Pollution

PI: Joel Schwartz
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EPA Grant Number: R834798-01

Project Summary:

Objectives: In this Project we will investigate the acute and chronic effects of air pollution on cognitive and neurological impairments, systemic inflammation, and vascular dysfunction. We will determine how these effects differ depending on the composition of multipollutant mixtures and the source contributions to PM composition. We will then ascertain the level of increased effects in susceptible and vulnerable subpopulations by examining modifying factors of obesity, diabetes, diet, socioeconomic position, and psychosocial stress.

Approach: Project 2 will build on our previous success using the Normative Aging Study (NAS) cohort, a large prospective cohort living in Eastern Massachusetts, and expand to make use of its extensive characterization for cognitive performance and psychosocial stress. With so much data already collected in this cohort, we can look at health effects longitudinally, where subjects act as their own controls. This reduces the potential for confounding while also increasing power. Our investigation of the health effects of air pollution will use our novel exposure approach to examine effects of individual pollutants, multi-pollutant mixtures, and sources. Under our current EPA Center grant, we developed and validated a spatio-temporal model for Black Carbon (BC) in the greater Boston area. Building on that success, we will now add a spatio-temporal model for O_3 to capture the spatial heterogeneity of exposure in the cohort study region, and we will estimate spatio-temporal variations in $PM_{2.5}$, and longer term variations in composition of air pollution, as described in the Exposure core. Using these improved exposure models will allow us to extend previous findings to understand the impact of different components and combinations of air pollutants on different aspects of health. In combination with Project 1 and 5, we will examine these exposures across a spectrum from biomarker to mortality, and in combination with Projects 3 and 4, across the lifecourse. Finally, we will examine the differential effects due to factors of susceptibility and vulnerability.

Expected Results: We have already reported different associations of traffic vs. secondary particles and ozone with different endpoints. With better exposure characterization and longer follow-up we will identify the key aspects of pollution that drive the association with cognition, inflammation, and vascular function. We will also determine the extent to which susceptibility factors, such as obesity, diabetes, and diet, modify these associations. This is critical for risk assessment, and will grow in importance as the prevalence of these conditions increases. Developing evidence suggests that stress and socioeconomic position may modify these health outcomes, and we will investigate the extent of these effects as well.

Project 3: Identifying the Cognitive and Vascular Effects of Air Pollution Sources and Mixtures in the Framingham Offspring and Third Generation Cohorts

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EPA Grant Number: R834798-01

Project Summary:

Objectives: Long- and short-term exposures to ambient air pollution are associated with adverse acute and chronic cardiovascular and perhaps cognitive function, but these effects are poorly understood. Using data from the Framingham Offspring and Third Generation Cohorts, well-characterized populations that have not been previously investigated in association with ambient environmental exposures, we will: (1) determine whether long-term exposures to ambient pollutants and mixtures are associated with cognitive impairment and cognitive interference; (2) test whether short-term and long-term exposures to pollutants, mixtures and sources are associated with acute and chronic vascular and endothelial function; and (3) consider whether markers of biological susceptibility and vulnerability differentially influence these associations, allowing us to identify subpopulations at increased risk for harmful effects of air pollution.

Approach: Exposures will be assigned using data from the Harvard School of Public Health Boston Supersite, a network of New England regional sites, rotating monitors, and satellite aerosol optical depth data. This information will be used to obtain predictors for linear regressions with covariate-adjusted models for cognitive outcomes (MMSE, CERAD Word List Memory and Victoria Stroop test) as well as vascular measures (blood pressure, brachial artery diameter, flow mediated dilation, digital pulse amplitude). Cross-product terms will be used to test susceptibilities and vulnerabilities.

Expected Results: We will estimate health risks associated with short- and long-term exposure to individual air pollutants, sources and air pollution mixtures within the Framingham Offspring and Third Generation populations. We will address which individual and area-level factors, measuring vulnerability, susceptibility, and individual air pollutants, sources and mixtures, are the major determinants in explaining spatial and temporal variability of the health risks. Also, we will be able to add to data addressing the effects of pollutants on the life course examined in Project 2: the Normative Aging Study by investigating cognitive performance and vascular function in populations of middle- and older-aged men and women.

Project 4: Longitudinal Effects of Multiple Pollutants on Child Growth, Blood Pressure and Cognition

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EPA Grant Number: R834798-01

Project Summary:

Objectives: Elevated blood pressure, reduced cognition, behavioral problems, and abnormal somatic growth are significant burdens on individuals, their families and society. We hypothesize that prenatal and postnatal pollution exposures (individual pollutants, sources, or mixtures) will lead to adverse changes in somatic growth, increased blood pressure, reduced cardiovascular fitness, and reduced cognition in children. The strength of the chronic and acute effects of individual pollutants on our outcomes will vary by source and mixture, as well as the timing of prenatal and postnatal exposures. Increased vulnerability or susceptibility to pollution effects on these adverse health outcomes will also result from socioeconomic disparities, stress and violence, environmental tobacco smoke, and reduced maternal and child omega-3 fatty acid intake measured in the prenatal as well as postnatal periods.

Approach: We will test these hypotheses using Project Viva, a unique ongoing pre-birth cohort of over 1,300 children from Greater Boston with longitudinal repeated measures of somatic growth, blood pressure, and cognition. Families were recruited between 1999 and 2002, during the first trimester of pregnancy. Primary longitudinal growth outcomes for Project Viva will include weight-for-length z-score and change in weight-for-length (birth through to age 2); body-mass index z-score and change in body-mass index (2 yr through 10 yr of age). Blood pressure is measured at birth, 6 months, 3 yr, and 7 yr; cardiovascular fitness is assessed by Step Testing at 7 yr. Cognition is assessed as visual memory at 6 mo, 3 yr and 7 yr; language at 3 yr and 7 yr; intelligence at 7 yr; and behavior at 7 yr. Chronic systemic inflammation is a well-documented risk factor for high blood pressure and atherosclerosis, and dysregulation of growth. Our Secondary Aim is to explore the effects exposures to individual pollutants, sources, and mixtures on intermediate immune and endocrine responses, including cord blood mononuclear cell (CBMC) lymphoproliferative responses, and innate (IL-6, TNF-α), adaptive Th1(IFN-γ), and Th2(IL-13) CBMC responses to stimulation with the mitogen PHA; dust mite, and cockroach allergen; allergic sensitization (3 and 7 yr) and inflammation-related adipokines (leptin and adiponectin) levels (birth, 3 and 7 yr).

Expected Results: Cognitive deficits and child behavior problems not only impose costs and burdens on children and their families, but also on their school systems. The origins of adult diseases, including elevated blood pressure are in childhood, and environmental controls in childhood may significantly reduce the risk of adult cardiovascular and neurovascular diseases. Therefore, identification of individual pollutants, pollution sources or mixtures that influence childhood blood pressure, cognition and growth is important for regulation and for child and future adult health.

Project 5: A National Study to Assess Susceptibility, Vulnerability, and Effect Modification of Air Pollution Health Risks

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EPA Grant Number: R834798-01

Project Summary:

Objectives: The proposed research responds directly to four of the research questions posed in the EPA solicitation: 1) What are the explanations for regional and temporal differences in air pollution risk? 2) What subpopulations are at increased risk? 3) How can the health effects of PM be better understood in a multi-pollutant context? 4) What is the exposure-response relationship for these sources and mixtures? To address these we will conduct a National study aimed at identifying factors that explain the heterogeneity of health risks associated with air pollution exposure. We hypothesize that such factors include medical and social conditions, conditions that modify exposure, and differences in pollution composition that modify exposure toxicity. Moreover, we hypothesize that the relevant factors vary among different health outcomes. Our research will be fully interactive with the other Center projects. Our previous results (e.g. diabetic susceptibility) have guided their analyses, and their results have generated specific hypotheses that we will test. We have 3 objectives. In Aims 1 and 2, we will conduct national studies of short- and long-term exposures to individual pollutants, sources, and mixtures. A main focus of our Center is to study established cohorts (NAS, Framingham, and Viva) in Massachusetts and surrounding states using novel, validated approaches to assess exposure. In Aim 3, we will complement those cohort studies, by establishing a cohort of 2.3 million Medicare enrollees residing in the same region and following its members prospectively for cause-specific hospital admissions and mortality for the period 2000-2014, and also by studying all live births in Eastern MA, geo-coded to exact address and followed for adverse birth outcomes.

Approach: We will use the largest available collection of national datasets including: 1) daily time series data of mortality and hospital admissions for thousands of zip codes in the US; 2) a cohort of 12 million Medicare enrollees followed prospectively for cause-specific hospital admission and death during the period 2000 to 2014; 3) a comprehensive collection of individual and area-level modifying factors; 4) exposures to individual pollutants, mixtures, and sources developed by the Biostatistics and Exposure cores.

Expected Results: Identifying factors that explain heterogeneity of risks will help to identify: 1) the populations that are more susceptible/vulnerable to air pollution; and 2) the emission sources, pollutants and pollutant mixtures that are more toxic. The characterization of susceptibility factors, such as age, gender, race, and pre-existing health conditions will inform research on biological mechanisms. The identification of the most harmful air pollution sources and components can aid decision-makers in developing targeted air quality regulations.

CORE: Exposure

EPA Grant Number: R834798-01

Project Summary:

Objectives: Current understanding of air pollution effects on human health has been limited by the inability of available analytical methods to assess exposure to ambient multi-pollutant mixtures, which encompass both physico-chemical and spatio-temporal complexity. To address this problem, the Exposure Core will develop and employ new methodologies to assess short- and long-term exposures to individual pollutants, sources and mixtures, permitting us to assess pollution effects on human health outcomes for our New England Cohorts (Projects 2-4) and National Study (Project 5). In addition, these methodologies will be made available to researchers outside the Center. This Core unites our research agenda, bringing all human Projects together to address a common set of exposure assessment-driven hypotheses. Accordingly, we have designed the Projects such that each of the three Cohorts and the National Study will assess the effects of the same six exposure metrics (short- and long-term exposures to individual pollutants, sources and mixtures) on cognitive and vascular health and inflammation, birth weight and growth, cause-specific hospitalization and mortality.

Exposures to individual pollutants will be based on direct measurements from local, regional and national networks combined with exposure models. Exposures to sources will be calculated using source apportionment techniques. Exposures to mixtures will be characterized using temporal clustering methodologies to group days with similar pollutant concentration profiles and using spatial clustering methodologies to identify groups of geographical locations, e.g. zip codes or counties, with similar pollutant concentration profiles.

Our approach to exposure assessment will employ: 1) the use of air pollution data collected by local and regional monitoring sites; 2) the use of satellite Aerosol Optical Depth (AOD) data to estimate spatial pattern of PM2.5 levels; 3) the development of clustering algorithms to identify profiles of air pollution mixtures; and 4) the use of state-of-the-art spatiotemporal and long-term spatial exposure models.

To assess exposures within the New England Region we will characterize both temporal and spatial patterns of pollution. We will assess temporal patterns of exposures within the Region using data from our Boston Supersite combined with spatial patterns analyzed using spatial networks, satellite data and spatiotemporal statistical models. We will also assess exposures to pollutant sources and mixtures using this information.

This investigation will also include populations across the US, for which our exposure assessments will be based on data from national monitoring networks. Time series analysis will be based on nearest-monitor air pollution data. In addition to assessing exposures to individual pollutants in the National study, for a subset of its geographical locations we will assess exposures to pollutant sources and mixtures.

CORE: Biostatistics

EPA Grant Number: R834798-01

Project Summary:

Objectives: The Biostatistics Core will provide centralized statistical and analytical expertise to all Center projects. Core Faculty are drawn from the Environmental Statistics Program within the Department of Biostatistics and the Exposure, Epidemiology, and Risk Program within the Department of Environmental Health at the Harvard School of Public Health. Core members provide expertise in the general statistical methods needed for the projects, such as linear regression and ANOVA, correlated data analysis (including longitudinal and spatial data analysis), measurement error, semiparametric and nonparametric (smoothing) models, meta-analysis, structural equation models, and Bayesian data analysis.

The Biostatistics Core will provide: 1) support for statistical analysis for all five proposed Projects, including, design consultation and analytical work; and 2) training for investigators in statistical issues needed for the data analysis and in SAS and R software. In addition, Core activities will include mission-related methodological research to develop needed statistical tools when existing methodology does not fully address the scientific question of interest.

Power and sample size calculations are critical components in all the Projects. Prospective calculations will ensure that Center project designs afford high power to detect meaningful differences. Core investigators have worked closely with Center investigators to determine effect sizes of interest and to calculate the numbers of samples necessary to achieve a desired level of power, usually 80% and 90%.

To the extent allowable by design and outcome commonalities among the five Projects, Core investigators will ensure that a unified approach to modeling strategy and choice of data transformations is applied to all Center data. Statistical analyses will apply appropriate exploratory data analysis techniques, such as univariate explorations of the data, distributional checks, and outlier identification to data from all projects. Residual analysis and other model diagnostics will be routinely used to confirm model fit, identify possible nonlinear relationships between predictors and outcomes, and identify highly influential data points. Once the data have been checked and modeling assumptions verified, primary analysis methods will include ANOVA and regression techniques, with the particular form of the outcome and correlation structure of the data dictating the particular method. The main analytical methods will be linear models/generalized linear models, semi-parametric regression modeling (smoothing), mixed/multivariate models for correlated responses, growth curve modeling, and Bayesian hierarchical models.

Development of new statistical methods (including software development and dissemination) will play an important role in the proposed Center Projects. These methods include spatio-temporal models for estimating exposures to PM, methods to address model uncertainty, novel distributed lag models, and exposure measurement error corrections. Future methodological development will focus on additional spatio-temporal modeling of pollution, the development of clustering methods to characterize exposure to complex pollution mixtures, and diagnostic tools to detect confounding.

CORE: Engineering

EPA Grant Number: R834798-01

Project Summary:

Objectives: The Engineering Core will support the Center by supplying the technologies required to conduct the proposed studies. The objectives of the Engineering Core will be to support the five projects of the proposed Center by: i) providing sampling and monitoring devices required for characterizing the spatial and temporal variability of pollutants within the study Region; ii) providing technology for generating and delivering inhalation exposures to animals; and iii) conducting sampling and analysis of particulate and gaseous pollutants.

Project 1: The Core will generate the test atmospheres for the animal exposure studies by integrating our ambient fine particle concentrator with the photochemical chamber and parallel plate membrane denuder developed for the TERESA studies. The exposures generated will include components of the Boston, MA, air pollution mixture both separately and in combination. These components will include CAPs, secondary gases, photochemically aged CAPs and secondary PM formed from ambient gases. In addition, the Core will be responsible for characterization of the animal exposures including: (i) integrated measurements of $PM_{2.5}$, elemental carbon (EC) and organic carbon (OC), sulfate (SO_4^{2-}), water soluble OC, trace elements, formaldehyde, acetaldehyde and VOCs; and (ii) continuous monitoring for $PM_{2.5}$, black carbon (BC), particle size distribution, particle number (PN), O_3, CO, and NOx.

Projects 2-5: The Core will conduct ambient monitoring, to characterize the spatial and temporal variability of particle and gas air pollutants within the study Region. To characterize the temporal variability of air pollution, the Core will operate the Boston HSPH Supersite. Measurements at the Supersite will include continuous and integrated PM_{10}, $PM_{2.5}$, $PM_{2.5-10}$, BC, EC/OC, SO_4^{2-} and NO_3^-. Additionally, continuous measurements will be conducted for PN, O_3, SO_2, NO_X, NO_2, and CO. To characterize the spatial variability of air pollutants within the study Region, the Core will operate a spatial network that will include a total of 40 outdoor monitoring sites. Monitoring will use one month durations, for each of four seasons, over a period of 4 years. At all of the spatial monitoring sites, the following pollutants will be measured: $PM_{2.5}$, BC, EC, OC, trace elements; PM_{10}, O_3, NO_2 and VOCs (benzene, toluene, ethylbenzene, and xylene). For all pollutants except VOCs, we will use the One Month Sampler, which is designed based on the multi-pollutant sampler (MPS) developed previously at HS.

CORE: Administration

EPA Grant Number: R834798-01

Project Summary:

Objectives: The Administration and Research Coordination Core will provide oversight, coordination and integration of the Center's activities within and between projects in the Harvard Medical area and also with EPA and the other PM Centers. This Core will be responsible for administration and organization, fiscal management, research management, research integration, research co-ordination, oversight of data management between projects, and communication.

The Center Director and Deputy Director will be responsible for the overall administration and management of the Center. They will work in close collaboration with the Steering Committee consisting of the Research Project and Core leaders. An external Science Advisory Committee will provide annual review and guidance on progress and priorities. Research integration will be achieved through regular meetings of a Working Group on Air Pollution Health Effects, a Work in Progress Seminar, a Journal Club, and Center Workshops. In addition, research activities will be integrated across the other Centers through regular Director's teleconferences and annual meetings of the Consortium of EPA Centers.

A major strength of our current Center's program has been an ability to redirect research to respond to recent findings and specific EPA needs. Thus, we have an established system in place to continually review and redirect Center research. The Center Steering Committee will continuously monitor research progress and developing research issues. The Center Investigators will present results and progress annually to the external Science Advisory Committee and will seek guidance on research priorities. In this application, we present five proposed research projects which have been defined by this process as providing cutting edge approaches to our central topic and theme, which are the health effects of air pollution mixtures across life stages. Each Project will be monitored and evaluated for progress and relevance, and may be modified or replaced over the five years of Center support.

The final objective of the Center is to make the results of this research available through peer-reviewed scientific publications, and also to disseminate our findings in ways that are accessible to policy makers and the lay public. To this end we will present Center results in scientific conferences, hearings and other public forums, and will maintain an informative website that presents our results in accessible formats and provides links to detailed results.

This Core is expected to provide the day to day administrative needs of center and to create an atmosphere of scientific cooperation and collaboration resulting in significant advancement and dissemination of scientific knowledge.