Request for Applications

HEALTH EFFECTS INSTITUTE

January 2014

Winter 2014 Research Agenda

RFPA 14-1 Enhancing Near-Road Exposure Assessment Through Characterization of Non-tailpipe and Tailpipe Emissions Near Urban Roads and in Tunnels

RFA 14-2 Walter A. Rosenblith New Investigator Award

The Health Effects Institute is a nonprofit organization chartered in 1980 as an independent research organization to provide high-quality, impartial, and relevant science on the effects of air pollution on health. To accomplish its mission, the Institute

- Identifies the highest-priority areas for health effects research;
- Funds and oversees the conduct of research projects;
- Provides intensive independent review of HEI-supported studies and related research;
- Integrates HEI's research results with those of other institutions into broader evaluations; and
- Communicates the result of HEI research and analyses to public and private decision makers.

Typically, HEI receives its core support from the U.S. Environmental Protection Agency and from the worldwide motor vehicle industry. Frequently, other public and private organizations in the United States and around the world also support major projects or certain research programs. HEI has funded more than 330 research projects in North America, Europe, Asia, and Latin America, the results of which have informed decisions regarding carbon monoxide, air toxics, nitrogen oxides, diesel exhaust, ozone, particulate matter, and other pollutants. These results have appeared in the peer-reviewed literature and in more than 260 reports published by HEI.

HEI's independent Board of Directors consists of leaders in science and policy who are committed to fostering the public–private partnership that is central to the organization. The Health Research Committee solicits input from HEI sponsors and other stakeholders and works with scientific staff to develop a Five-Year Strategic Plan, select research projects for funding, and oversee their conduct. The Health Review Committee, which has no role in selecting or overseeing studies, works with staff to evaluate and interpret the results of funded studies and related research.

All project results and accompanying comments by the Health Review Committee are widely disseminated through HEI's Web site (*www.healtheffects.org*), printed reports, newsletters, and other, publications, annual conferences, and presentations to legislative bodies and public agencies.

THE HEALTH EFFECTS INSTITUTE – WINTER 2014 RESEARCH AGENDA

Table of Contents

[1] Section has been revised since the previous Winter 2013 RFA booklet

INTRODUCTION

This booklet contains the Winter 2014 Research Agenda of the Health Effects Institute (HEI). We thank you for your interest in HEI and its research program. The area of research for which the Institute is requesting applications at this time is described below. The booklet also describes the application submission and evaluation processes and provides information on HEI management of funded studies. HEI has recently expanded the Quality Assurance / Quality Control procedures for HEI studies. Prospective applicants should become familiar with these procedures as they develop the application.

REQUEST FOR PRELIMINARY APPLICATIONS 14-1: ENHANCING NEAR-ROAD EXPOSURE ASSESSMENT THROUGH CHARACTERIZATION OF NON-TAILPIPE AND TAILPIPE EMISSIONS NEAR URBAN ROADS AND IN TUNNELS

The RFPA solicits applications for research in two areas that complement current and past research that HEI has supported to improve assessment of exposure to motor vehicle emissions: A) Characterization of the composition of non-tailpipe particulate emissions from the current vehicle fleet and their contribution to total near-road particulate matter, and B) Characterization of emissions changes as a result of changes in engine and emission control technologies and fuels in tunnel studies. It provides funding for 1- to 2-year studies.

The submission and review of applications for RFPA 14-1 will entail a two-stage process:

- Interested scientists should submit a preliminary application by **MARCH 3, 2014**. The HEI Research Committee will discuss the preliminary applications and will provide feedback within 2 to 3 weeks after submission.
- Full applications (by invitation only) should be submitted no later than **APRIL 25, 2014**. Full applications will be reviewed by the Research Committee in late June 2014.

REQUEST FOR APPLICATIONS 14-2: WALTER A. ROSENBLITH NEW INVESTIGATOR AWARD

The purpose of this award, described on pages 13–14, is to bring new, creative investigators into active research on the health effects of air pollution. It provides three years of funding to an investigator with outstanding promise at the Assistant Professor or equivalent level for a small project relevant to HEI's research interests. For information on HEI's current research priorities, applicants should consult *Appendix A*, which contains portions of HEI's current strategic plan.

HEI expects to provide one award from this RFA. The evaluation process for these applications will consider the qualifications and background of the applicant, the quality and relevance of the research proposal, and the research environment of the applicant.

- Interested scientists should submit a Letter of Intent and Curriculum Vitae by **APRIL 22, 2014**.
- Full applications should be submitted no later than **JUNE 3, 2014**.

THE HEALTH EFFECTS INSTITUTE

WHAT IS HEI?

HEI is a public–private partnership established in 1980 to provide decision makers, scientists, and the public with high-quality, impartial, and relevant scientific information that helps answer key questions about the health effects of emissions from motor vehicles and other sources in the environment. The idea for the Institute grew from discussions between leaders of the U.S. Environmental Protection Agency (EPA) and the automotive industry concerning the certification requirements in the 1977 Clean Air Act Amendments. As a result, EPA and industry representatives cooperated to establish an independent institution to carry out the much-needed health effects research. The intent of the Health Effects Institute has been to develop the scientific facts concerning health effects carefully and credibly so that controversy about the facts themselves will be removed from the adversarial agenda and the debates over clean air can instead focus on national policy issues.

HEI is an unusual model of government-industry collaboration in support of research. The Institute receives its core funds from the EPA and from the worldwide motor vehicle industry. HEI has also received additional support in several areas from a variety of other public and private sponsors. On the government side, these include the Federal Highway Administration, the California Air Resources Board, and the Department of Energy. On the industry side, these include the oil, steel, and utility industries. HEI's activities in Asia have received support from the US Agency for International Development, the Asian Development Bank, and the William and Flora Hewlett Foundation. The Institute has developed consultation processes with its sponsors and others to help focus its research priorities. However, none of the contributors has control over the selection, conduct, or management of HEI studies, and HEI makes no recommendations on how to apply research to regulatory policy.

The Institute's autonomy is supported, even beyond the statements in its charter, by the integrity and commitment of both its scientific leadership and its Board of Directors. Subject to the approval of the Board of Directors, the work of the Institute is carried out by two external and independent Committees for research and review, each consisting of distinguished scientists knowledgeable about the scientific issues inherent to investigating the health effects of air pollutants. HEI's science staff works with Committee members in carrying out the work of the Institute.

HOW DOES HEI WORK?

After seeking advice from HEI's sponsors and others interested in its work, the HEI Research Committee determines the research priorities of the Institute. When an area of inquiry has been defined, the Institute announces to the scientific community that applications are being solicited on specific topics by issuing requests for applications such as those in this booklet. Applicationsare reviewed first for scientific quality by appropriate experts. They are then reviewed by the HEI Research Committee both for quality and relevance to the goals of the research program as outlined in the Strategic Plan.

Before a study is recommended for funding, there is often a negotiation period in which the investigators may be asked to address the reviewers' comments or modify the study design or budget. Studies recommended by the Research Committee undergo final approval by the Board of Directors, which reviews the procedures, independence, and quality of the selection process. HEI's mechanism for providing funds to its investigators is a cost-reimbursement contract (Research Agreement) containing a Statement of Work, which is a description of the work to be performed in each contract year, and a budget. Because HEI is sensitive to the fact that research may generate unexpected results leading to a need for a change in the scope of work, HEI's contracts can be amended upon agreement by both parties.

During the course of each study, the Research Committee and scientific staff maintain close contact with HEI-funded investigators by means of progress reports, site visits, workshops, and the HEI Annual Conference. The 10-month progress report serves as the basis for contract renewal for multi-year projects. A site visit is conducted to many investigators' laboratories, not only to assess the conduct of the study, but also to provide an opportunity for discussion and exchange of ideas. At the Annual Conference, HEI investigators, Research Committee and Review Committee members, HEI staff, representatives of sponsor organizations, invited scientists, and other attendees meet to share information and develop new ties to strengthen the HEI community of scholars. A more detailed description of the relationship between HEI and investigators can be found on pages 21–25.

In order to fulfill its mission of providing timely, high-quality research results for decision makers, HEI has developed a rigorous review process to evaluate results of the research it funds. When a study is completed, the investigator is required to submit a comprehensive final report. The HEI Review Committee, which has no role in the review of applications or in the selection or conduct of projects, assesses the scientific quality of each completed study and evaluates its contribution to unresolved scientific questions. The investigator's Final Report and a Commentary of the Review Committee are published together by HEI. Additionally, all HEI investigators are urged to publish the results of their work in the peer-reviewed literature. More information on the final report and review process can be found on pages 23–24.

THE HEI RESEARCH PROGRAM

The HEI research program has addressed many important questions about the health effects of a variety of pollutants, including nitrogen oxides, ozone, particulate matter, carbon monoxide, diesel exhaust, several air toxics (aldehydes, benzene, 1,3-butadiene), methanol, and oxygenates added to fuel. HEI has funded studies to understand the mechanisms of diseases, to develop better methods to assess health effects and determine exposure and dose, and to address issues common to many pollutants. HEI also has funded studies to evaluate the effectiveness of air quality regulations towards improving public health, an area known as health outcomes or accountability research. The program has included modeling, in vitro, and animal studies, controlled human exposure studies, and epidemiologic studies. The choices of which pollutants to study or scientific questions to investigate have been made based on many considerations, including analysis of the scientific uncertainties and regulatory needs regarding health effects of specific pollutants as well as issues raised by HEI's sponsors. HEI has, on some occasions, produced special reports to evaluate the state of existing science in areas related to policy and to determine research needs in new areas.

In April 2010, after extensive consultation with sponsors, scientists, and other stakeholders, HEI issued a new five-year plan, the *HEI Strategic Plan for Understanding Health Effects of Air Pollution 2010–2015*, which describes research and review priorities and plans for implementing them. HEI has identified the following specific activities by applying next generation multi-pollutant approaches to conventional pollutants, and at the air quality – climate nexus. The 2010–2015 Strategic Plan describes four priority areas:

· **Multi-Pollutant Research on Exposure, Epidemiology, and Toxicology**. In 2010, HEI initiated research to test the effects of ozone on the cardiovascular system (RFA 10-1). In addition, HEI will pursue research to further understand toxicity among air pollutants that can be important climate agents; to examine multi-pollutant exposure and health in high exposure situations; and to fill key gaps identified in HEI Special Report 17, *Traffic-Related Air Pollution: A Critical Review of the Literature on Emissions, Exposure, and Health Effects* (2010).

· **Emerging Technologies and Fuels**. HEI expects to initiate research and literature review activities to provide time-sensitive information about the full range of emissions and effects of new technologies and fuels that are being driven by climate change, energy efficiency, and air quality. Targeted research to fill key knowledge gaps may include emissions from the use of ethanol and other alternative fuels; evaluation of NO_x aftertreatment technologies for advanced diesel engines; technological advances driven by fuel efficiency and their potential effects on ultrafine particle emissions; electric and hybrid vehicles; studies of metals in fuel additives; and life cycle issues with a special focus on their implication for health effects.

· **Measuring the Health Outcomes of Air Quality Actions**. In 2011, HEI initiated a second wave of research on accountability, with a focus on national scale programs and efforts to improve air quality in ports areas. Key research recommendations are outlined in HEI Communication 15, *Proceedings of an HEI Workshop on Further Research to Assess the Health Impacts of Actions Taken to Improve Air Quality* (2010). Specific areas of regulation and intervention that remain of interest to HEI include the following: the impacts of systematic introduction of new fuels and technologies over time (e.g. biofuels); assessing the effects of regulatory interventions on populations exposed to multiple sources in areas with higher levels of pollution (e.g. ports and urban hot spots); and systematic efforts to assess actions aimed at reducing exposure of susceptible populations.

· **An International Perspective**. HEI will continue to pursue research questions related to air pollution, climate, and health in a global context, through coordinated assessments of research across multiple continents. Selective new research will include studies on the potential relationship between exposure to air pollution and children's health outcomes, including acute lower respiratory infections as well as reproductive or developmental health effects. Additional studies will be sought on the intersection of air

quality, climate, and health; and on long-term effects in existing cohorts (if technically feasible, and contingent on additional funding becoming available).

In addition, HEI expects to pursue important **cross cutting issues** in all of its efforts, including selected *sensitive subpopulations* and *innovation and validation*. Sensitive populations include the elderly, those with asthma, diabetes, cardiovascular, and other non-cancer diseases; those of lower socioeconomic status; and — in coordination with larger national efforts, such as the Children's Health Study — the young. Regarding innovation and validation, HEI has done much to advance innovative techniques for improved exposure assessment, statistical analysis, and toxicology — especially, to develop innovative methods and then to test and validate those methods to ensure they provide high quality information to inform better decisions. Key areas of interest are enhanced statistical techniques, new methods for toxicity testing, new biomarkers of health effects, and enhanced public access to data.

For more detailed information, please see *Appendix A*, which provides sections from HEI's current Strategic Plan on research priorities and plans for implementing them. The entire plan is available on HEI's website, *www.healtheffects.org/funding.htm*. At this time, a new Strategic Plan for 2015-2020 is under development and will be released early in 2015.

The problems associated with the evaluation of the health effects of mobile source emissions are complex, as researchers who have devoted their efforts to this field are well aware. The resolution of questions pertaining to the effect on health of relatively low levels of these complex mixtures is a challenging area of scientific investigation. HEI seeks to develop a community of scientists and scholars who can generate new collaborations and fresh approaches to the problems of air pollution. To this end, HEI has funded both established and early-career investigators, attracting a number of scientists into this area who did not work in it before.

RFPA 14-1: ENHANCING NEAR-ROAD EXPOSURE ASSESSMENT THROUGH CHARACTERIZATION OF NON-TAILPIPE AND TAILPIPE EMISSIONS NEAR URBAN ROADS AND IN TUNNELS

INTRODUCTION

The Request for Preliminary Applications (RFPA) provides a mechanism for the HEI Research Committee to explore research areas that are of interest and compatible with HEI's research mission and complement the current research program, but fall outside major targeted Requests for Applications.

With this focused RFPA, HEI seeks preliminary applications for research in two areas that complement current and past research that HEI has supported to improve assessment of exposure to motor vehicle emissions:

A) Characterization of the composition of non-tailpipe particulate emissions from the current vehicle fleet and their contribution to total near-road particulate matter (PM);
B) Characterization of emissions changes as a result of improvements in engine and emission control technologies and fuels in tunnel studies.

Preliminary applications will be reviewed by the Research Committee in **March 2014**. Applicants with promising ideas will be asked to submit a full application, which will be evaluated by several external reviewers before consideration by the Research Committee. More details about the procedures can be found in the section *RFPA 14-1 Application Process, Deadlines, and Evaluation* on pages 11-12.

STUDY DURATION AND BUDGET GUIDELINES FOR RFPA 14-1

HEI encourages interested applicants to submit preliminary applications for 1 to 2-year projects. The HEI Research Committee will generally not consider studies of longer duration, unless the applicant very clearly justifies the need for the extra time. Preparation of the final report should be included in the budget of the final year of the study. A total of up to $1.2 million will be available for this program. HEI anticipates that 2-4 applications will be funded.

RFPA 14-1A: EVALUATING THE CONTRIBUTION OF NON-TAILPIPE PM EMISSIONS TO NEAR-ROAD CONCENTRATIONS

Background and Rationale

In 2010, HEI published a Special Report on traffic-related air pollution (HEI Panel on the Health Effects of Traffic-Related Air Pollution 2010). The Report stated that "emissions from tire wear, brake wear, and resuspended road dust should not be overlooked in the assessments of vehicle emissions and their effects on health." Among the elements in non-tailpipe PM emissions, transition metals, such as copper (Cu), iron (Fe), and zinc (Zn), are of toxicological interest because these transition metals may play a role in the pro-inflammatory effects of PM. A report by the HEI Special Committee on Emerging Technologies (2011) also drew attention to these issues. In 2013, HEI issued RFA 13-1, *Improving Assessment of Near-Road Exposure to Traffic Related Pollution,* seeking studies to improve assessment of near-road exposure to traffic related pollution. The RFA noted that "it would be useful to quantify the contribution and impact of each of the various sources [i.e., tailpipe and non-tailpipe] on real life exposures." However, none of the studies funded under RFA 13-1 will specifically address non-tailpipe emissions. With RFPA 14-1, HEI seeks to address this research gap.

With the significant reduction of tailpipe PM emissions from new technology diesel vehicles, interest in non-tailpipe emissions of motor vehicles is increasing. It has been estimated that as much as 50% of the traffic-generated PM_{10} near some major roads may be attributable to non-tailpipe emissions (Denier van der Gon et al 2013). Following current trends — with regulations targeted almost exclusively to tailpipe emissions and an increase in vehicle miles traveled — it is possible that non-tailpipe PM emissions may exceed tailpipe PM emissions at some point in the future (Rexeis and Hausberger 2009). Thus, there is interest in understanding how these trends would affect exposures of individuals living near major roads.

Non-tailpipe PM emissions are formed from mechanical processes, in contrast with particles from tailpipe emissions, which are formed during the combustion process. There are three main sources of non-tailpipe PM emissions from on-road vehicles: those generated by abrasion of brakes and tires, those generated by abrasion of the road surface, and those resuspended from the road surface (called road dust). As a result, particles from non-tailpipe sources differ from particles from tailpipe emissions both in composition and size distribution: their size is generally larger than tailpipe particles, and they have a higher metallic content (including species such as barium [Ba], Cu, Fe, and Zn that are derived mostly from brake lining) and less carbonaceous material (Denier van der Gon et al 2013; HEI Special Committee on Emerging Technologies 2011). Although non-tailpipe particles are predominantly in the coarse fraction of PM, they are present in smaller size fractions as well.

Like tailpipe emissions, the concentration of non-tailpipe emissions near the road is influenced by meteorology, vehicle type, traffic composition and conditions, and local dispersion characteristics. Another feature that complicates exposure assessment of the non-tailpipe emissions is that various manufacturers of brakes and tires use different materials, but their composition is proprietary and their formulations change frequently. Additionally, the composition of materials used to build roads, their wear, and the contribution of dust from surrounding areas is variable. Interactions among the different non-tailpipe sources make the identification of unique markers extremely challenging; for example, brake or tire particles may deposit on the road surface and subsequently be resuspended as part of road dust. Road dust also includes biological components (such as pollen), chemicals from various sources, and debris of various types and from myriad sources. Previous studies have sought to distinguish the different non-tailpipe PM emissions by identifying unique chemical markers of non-tailpipe particles in some locations; other studies also have attempted to determine the contribution of the individual sources to ambient PM. However, a lack of detailed source profiles makes the conclusions of these studies uncertain. More details on some of the issues discussed here can be found in Thorpe and colleagues (2008), Denier van der Gon and colleagues (2013), and HEI Special Committee on Emerging Technologies (2011).

Objectives of RFPA 14-1A

The overall objective of RFPA 14-1A is to obtain data on the characteristic and contribution of non-tailpipe PM emissions to total PM in the proximity to roads (up to 500 m) that could be applied to future exposure and health assessment studies. The specific objectives of this RFPA are as follows:

- Characterize the size distribution and composition of tailpipe and non-tailpipe particle emissions. The focus should be on the current vehicle fleet near different types of major (urban) roads with different traffic conditions. In addition, measurements should be taken at a representative background location(s) to allow for comparisons and possibly at different distances from the roads;
- Improve and standardize sampling methodologies to characterize non-tailpipe emissions under real-world conditions;
- Identify and validate exposure surrogates (based on a single PM component or a combination of components) for the different sources of non-tailpipe PM emissions;
- Characterize and compare emissions of different types of in-use brake lining and/or different tires in a laboratory setting;
- Apply source apportionment methods to evaluate the contribution to near-road PM concentrations of non-tailpipe emissions relative to tailpipe emissions;
- Identify the most important variables that explain spatial and temporal variability of the various sources of non-tailpipe emissions (such as traffic composition, speed, meteorology, or geography).

HEI encourages applicants to address more than one objective, if feasible within the budget constraints, and to use existing data sets or add on to ongoing studies if possible.

RFPA 14-1B: TUNNEL STUDIES TO CHARACTERIZE EMISSIONS FROM THE CURRENT FLEET OF MOTOR VEHICLES

Background and Rationale

Emissions from motor vehicles have changed substantially over the last few decades because of new fuels, changes in engine designs, and improved emission control technology. More changes are expected as engine and emission control technologies continue to evolve and new fuels and blends are introduced. For example, as the HEI Special Committee on Emerging Technologies (2011) pointed out, the new gasoline direct-injection

engines — which offer improved fuel efficiency — may lead to higher emissions of ultrafine particles and perhaps also PM in general. The use of ethanol blends has been shown to lead to increased emissions of carbonyl compounds (acetaldehyde, acrolein, and others) and ethanol itself, and to decreases in other compounds. On the other hand, exhaust after-treatment devices have reduced PM emissions from diesel-powered vehicles, and the required selective reduction catalysts can reduce nitrogen dioxide (NO 2), if used and operated optimally. As these technologies and fuels are beginning to have a substantial market share, it is important to obtain a better understanding of changes in emissions from on-road fleets (HEI Special Committee on Emerging Technologies 2011). This is also an important first step in addressing HEI's interest in measuring the health outcomes resulting from actions taken to improve air quality (Health Effects Institute 2010).

To evaluate how recent and future changes affect the emissions of the motor vehicle fleet, there is a need for detailed characterization of emissions of the fleet over time. Such measurements could provide useful information and also be compared with previously collected data and serve as a baseline for future comparisons. Roadway tunnels offer a practical opportunity to study emissions from the on-road fleet of motor vehicles in a well-defined, quasi-closed system not affected by other combustion sources.

HEI previously supported two tunnel studies that are described in HEI Research Report 107 (Health Effects Institute 2002). Dr. Gertler studied PM emissions in the Tuscarora Mountain Tunnel located on the Pennsylvania Turnpike. Of particular interest in the Gertler study was the determination of changes over time in particulate and gas phase emissions by comparing the study results with those of previous studies conducted at the same tunnel. Dr. Grosjean characterized carbonyl emissions in the Tuscarora Mountain Tunnel and in the Caldecott Tunnel in California, which provided the opportunity to characterize emissions from light-duty and heavy-duty vehicles separately. In addition, HEI supported a study that analyzed metal emissions in both $PM_{2.5}$ and PM_{10} samples collected in the Kilborn and Howell Tunnels in Milwaukee, Wisconsin (Schauer et al 2006). Many other tunnel studies have been conducted in the United States as well as in other parts of the world, and have yielded important insights. For a recent review, see Kuykendall et al (2009), who identified approximately 50 studies conducted at more than 35 different tunnels around the globe.

Tunnel studies allow for characterization of emissions that are effectively the average from various vehicle types and could be conducted in different seasons or evaluate different traffic flow situations. In the past, tunnel studies have provided data on a wide variety of pollutants, including PM and organic and inorganic compounds in relation to 1) vehicle fleet composition (diesel vs. gasoline-fuelled vehicles), 2) driving patterns, including speed, 3) meteorology factors, including temperature, and 4) changes in emissions over time and implementation of new regulations and cleaner technologies. It is also well recognized that tunnel studies have limitations, such as a lack of information on emission factors from individual vehicles or vehicle characteristics, although it is possible that new monitoring devices can provide such information. Emissions in tunnels are also minimally subject to atmospheric and meteorologic processes (thus not completely reflective of ambient conditions) and the tunnel's unique configuration does not allow for easy generalization to the more common exposure situations of human populations. In addition, the fleet composition may depend on the location of the tunnel and driving conditions may not reflect those encountered on urban roads. Nevertheless, tunnel studies have their own advantages and provide unique information that is otherwise difficult to obtain. More information on tunnel studies can be found in Chapter 2 of the HEI Special Report, Traffic-Related Air Pollution: A Critical Review of the Literature on Emissions, Exposure, and Health Effects (HEI Panel on the Health Effects of Traffic-Related Air Pollution 2010).

Objectives of RFPA 14-1B

The overall objective of RFPA 14-1B is to characterize emissions of motor vehicles in roadway tunnels in the United States or elsewhere, including rapidly industrializing countries (e.g. China), preferably where previous studies have been performed to allow an evaluation of changes in emissions over time due to new technologies and fuels. The specific objectives of this RFPA are as follows:

- Characterize gaseous and particulate-phase emissions of motor vehicles from the current fleet, including both criteria and non-criteria pollutants;
- Analyze the emissions of motor vehicles in terms of specific characteristics of the current vehicle fleet (e.g. type, and model year of vehicles; fuels used, e.g. specific winter or summer time regional blends);
- Identify novel and unique markers for motor vehicles that could be used to separate different components of the fleet;

- Compare the emissions of the current fleet with emissions from previous fleets, preferably at the same location where earlier measurements were made with similar methods. Comparisons with estimates from emission models such as the California Air Resources Board's EMFAC and the Environmental Protection Agency's MOVES models would also be desirable.

Applicants should consider a multi-pollutant approach, with a clear scientific rationale for the choice of the measured pollutants. These may include PM mass and number, particle size distribution, chemical analysis of PM samples, as well as gaseous components, such as NO_2, air toxics (particularly carbonyls), and secondary aerosol precursors. Where feasible, studies should produce results from different tunnel locations and operating conditions, e.g. free-flowing highway tunnels as well as more urban, congested tunnels. Careful consideration should be given to comparison of the results in terms of changing emissions over time due to changes in technologies and fuels.

HEI encourages applicants to carefully document the tunnel characteristics so that the results can be compared with previous (if any) and future efforts in the same tunnel. We also encourage new approaches to document the vehicle fleet in detail, including the traffic volume, vehicle type, age, speed, fuels used, as well as monitoring devices and approaches that may allow emissions characterizations from individual vehicles. Finally, investigators may propose additional research questions to pursue that provide more insight into specific questions regarding the nature of the motor vehicle emissions in tunnels, for example the differentiation between tailpipe and non-tailpipe emissions.

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RFPA 14-1: APPLICATION PROCESS, DEADLINES, AND EVALUATION

The preliminary application process consists of two stages, a preliminary application followed by a full application (upon request only).

PRELIMINARY APPLICATION

Applicants should submit a preliminary application that provides the following information: scientific rationale, a brief description of the study aims, design and methods, statistical methods, and anticipated results. An estimated total budget and study duration (up to two years) should be provided. In addition, brief curricula vitae (CVs; maximum 2 pages per person) of the principal investigator and co-investigators should be provided.

Investigators should use the Preliminary Application Form to submit the preliminary application, which can be downloaded from *www.healtheffects.org/funding.htm*. The preliminary application must be no more than five pages in length (using 11-point font size and 1-inch margins; excluding references and CVs); it will be returned to applicants if it is longer.

Deadline for Preliminary Applications

Preliminary applications should be submitted by e-mail in PDF format to *funding@healtheffects.org* no later than **MARCH 3, 2014**, with a copy to Ms. Margarita Shablya (*mshablya@healtheffects.org*). HEI will acknowledge receipt of the application.

Preliminary Application Evaluation Process

Preliminary applications will be reviewed by the Research Committee. If the Committee expresses interest in the study, the investigator is requested to prepare a full application. The selection is primarily based on relevance of the proposed research to the objectives of the RFPA and the scientific merit of the preliminary application. Applicants will be informed whether or not to submit a full application within 2-3 weeks after the submission date.

For questions contact: Dr. Maria Costantini (*mcostantini@healtheffects.org*, +1-617-488-2302) or Dr. Hanna Boogaard (*jboogaard@healtheffects.org*, +1-617-488-2306)

FULL APPLICATION

Investigators invited to submit a full application should use forms F-1 to F-12 (see list on page 33) and consult the *Instructions for Completing the Application* found on pages 27–32. Application forms can be downloaded from *www.healtheffects.org/funding.htm*. Please note that the required font size is **11 point with 1-inch margins**. Full applications without pre-submission of a preliminary application will **not** be considered.

A full application will provide in-depth details on the study aims, design, rationale, methods, and statistical analyses. If data from other studies are going to be used, information on the type of data available (including the period, location, and frequency of when the measurements were taken) and quality assurance should be included. Investigators should also discuss whether they will need to obtain IRB approval. A letter from the investigator who owns the data should be submitted, stating his or her willingness to share the data with the applicant and with HEI, if requested (see Appendix D: *HEI Policy on the Provision of Access to Data Underlying HEI-funded Studies* on pages 55–56.)

Deadline for Full Applications

Full Applications for RFPA 14-1 should be submitted to *funding@healtheffects.org* no later than **APRIL 25, 2014**. The application should be in PDF format with a maximum file size of 20 MB.

After submission, please notify Ms. Margarita Shablya (*mshablya@healtheffects.org* or +1-617-488-2345) of your submission; do not attach the PDF documents to this email. HEI will acknowledge receipt of the application.

Full Application Evaluation Process

Full applications will be evaluated in two phases. First, external scientists selected for their relevant expertise will evaluate the applications according to the following criteria:

- Relevance of the proposed research to the objectives of the RFA.
- Scientific merit of the proposed study design, approaches, methodology, analytic methods, and statistical procedures.
- Personnel and facilities, including:
  - Experience and competence of the principal investigator and scientific staff,
  - Adequacy of effort on the project by scientific and technical staff,
  - Adequacy of facilities.
- Reasonableness of the proposed cost and appropriateness of the allocation of the requested funds.

Second, the Research Committee will evaluate the full applications with consideration of the reviewers' comments and of the ways the proposed research might improve the understanding of the specific problem under investigation. The Research Committee's recommendation about funding will also consider how studies complement each other in addressing the objectives of the RFPA within the available resources. The Research Committee makes final recommendations regarding funding of studies to the Institute's Board of Directors, which makes the final decision.

RFA 14-2: WALTER A. ROSENBLITH[1] NEW INVESTIGATOR AWARD

INTRODUCTION

HEI has established the New Investigator Award to provide funding for outstanding investigators who are beginning independent research. By providing financial support for investigators at this point in their careers, HEI hopes to encourage highly qualified individuals to undertake research on the health effects of air pollution. The candidates may have training and experience in any of the many branches of science relevant to air pollution.

Each award will be up to $150,000 per year with a maximum of $450,000 for three years in total costs to support a research project. The funds can be used to provide salary support for the investigator and supporting junior personnel as well as operating costs, including supplies and equipment. It is expected that the investigator will devote at least 25% of his or her time on the proposed research. HEI expects to provide one award from this RFA and make additional awards each year. For information on past awardees, please see the List of Awardees below.

HEI RESEARCH PROGRAM

Since 1983, HEI's research program has addressed a broad range of questions about the health effects of air pollutants derived from motor vehicle emissions, including aldehydes, carbon monoxide, methanol, nitrogen oxides, ozone, and particulate matter, including diesel particles and associated compounds. Several studies have addressed the effects of exposure to more than one pollutant. Research projects are often interdisciplinary in nature and span a range of scientific fields, including atmospheric science, epidemiology, exposure science, statistics, and toxicology.

In considering potential research topics, applicants should be aware of HEI's current areas of interest, as described in the HEI Strategic Plan for the Health Effects of Air Pollution 2010-2015 that was issued in April 2010. The plan emphasizes research on multi-pollutant effects, and at the air quality–climate nexus. The focus is on four key areas: (1) multi-pollutant exposure, epidemiology and toxicology research, (2) emerging technology and fuels, (3) research on the effectiveness of air quality actions to improve public health (air quality outcomes research), and (4) an international perspective.

Appendix A includes sections of the Strategic Plan that describe HEI's current research priorities and plans for implementing them. The entire plan is available on HEI's website, *www.healtheffects.org/funding.htm*. Appendix B provides a listing of HEI studies and reports, which gives information on the pollutants and issues in which HEI has been interested over the years.

Depending on the research question, HEI studies have used a wide range of designs: modeling, experiments with cell cultures, animal studies, controlled human exposure studies, and epidemiologic investigations. In all studies, accurate characterization of exposure is important. Because the ultimate goal of HEI's research is understanding effects in people, both human studies and studies to improve extrapolation from animals to humans are an important part of HEI's program. There are two cross-cutting issues that the HEI Research Committee specifically would like to emphasize in HEI-funded studies. The first is to identify and evaluate effects in susceptible groups that may respond at lower levels of exposure than "normal" participants; for example, the young or old, people of lower socioeconomic status, or those with pre-existing disease. Because the ultimate goal of research funded by HEI is to provide data that can inform regulatory decisions about air quality, as a second cross-cutting issue, HEI encourages the development of new methods and technologies that could be used later to provide data useful for regulatory purposes.

HEI encourages investigators to submit applications addressing these high priority research areas. However, HEI realizes that other areas of research may lead to results important to its mission. For this

[1] This award is named for Professor Walter A. Rosenblith (1913–2002), who served as the first Chair of HEI's Research Committee (from 1980 to 1989) and as a member of the HEI Board of Directors from 1990 to 1996. Professor Rosenblith's vision of science and standard of excellence enabled HEI to quickly develop a strong scientific program. At his urging, HEI developed a program that not only funds research that would contribute needed scientific information for regulation, but also research to strengthen the fundamental science related to environmental issues. Professor Rosenblith supported activities intended to attract people engaged in more basic scientific research so that they might bring new tools and new ideas to environmental questions.

reason, we will also consider particularly innovative or high quality applications in other areas that are relevant to the overall goals of HEI's program.

LIST OF AWARDEES

Year	*Awardee and Project Title*
1999	Francesca Dominici, Johns Hopkins University, Air pollution and daily mortality in a national sampling frame
2001	Quanxin Meng, Battelle Toxicology Northwest, Mutagenicity of stereochemical configurations of 1,3-butadiene epoxy metabolites in human cells
2002	Jamie Schauer, University of Wisconsin, Source apportionment and speciation of particulate matter to support exposure and health studies
2003	Michael Borchers, University of Cincinnati, T cell subpopulations regulate airway inflammation and injury following acrolein exposures
2004	Michelle Bell, Yale University, Assessment of the mortality effects of particulate matter characteristics
2004	Michaela Kendall, Uludag University, Turkey, Molecular adsorption at PM surfaces: a compelling PM toxicity mediation mechanism
2005	Jonathan Levy, Harvard School of Public Health, Using geographic information systems to evaluate heterogeneity in indoor and outdoor concentrations of particle constituents
2005	Timothy Nurkiewicz, West Virginia University, Pulmonary particulate matter exposure and systemic microvascular function
2006	Christopher Paciorek, Harvard School of Public Health, Integrating monitoring and satellite data to retrospectively estimate monthly $PM_{2.5}$ concentrations in the eastern United States
2006	Qunwei Zhang, University of Louisville, Activation of endothelial cells and gene expression in lungs following exposure to ultrafine particles
2007	Charles Stanier, University of Iowa, Development and application of a personal exposure screening model for size-resolved urban aerosols
2007	Yifang Zhu, Texas A&M University Kingsville, Assessing children's exposure to ultrafine particles from vehicular emissions
2008	Thomas Barker, Georgia Institute of Technology, Extracellular matrix stiffness associated with pulmonary fibrosis sensitizes alveolar epithelial cells
2008	Jiu-Chiuan Chen, University of Southern California, Particulate air pollutants, risk of cognitive disorders, and neuropathology in the elderly
2010	Jun Wu, University of California–Irvine, Adverse reproductive health outcomes and exposures to gaseous and particulate matter air pollution in pregnant women
2011	Juana Maria Delgado-Saborit, University of Birmingham, UK, Use of real-time sensors to assess misclassification and to identify main sources contributing to peak and chronic exposures
2011	Richard Peltier, University of Massachusetts, Amherst, Development of a new method for measurements of reactive oxygen species associated with $PM_{2.5}$ exposure
2012	Jason Surratt, University of North Carolina–Chapel Hill, Understanding the health effects of isoprene-derived particulate matter enhanced by anthropogenic pollutants

RFA 14-2: APPLICATION PROCESS AND DEADLINES

ELIGIBILITY REQUIREMENTS

Scientists of any nationality holding a PhD, ScD, MD, DVM, or DrPH degree or equivalent are eligible to apply. At the time of application the candidate should have two to six years of research experience after obtaining the highest degree and must be in an assistant professor or equivalent position at an academic or research institution. Evidence that the candidate's institution is prepared to make a tangible commitment to helping the awardee become established as an independent investigator is required as part of the application. Candidates should possess outstanding research potential. Evidence of this potential, in the form of written letters of support and the candidate's publication record, is an essential part of the application materials and will be valued equally with the scientific proposal.

Please note that an applicant who does not meet all eligibility requirements will not be considered for this award. HEI will not review applications from individuals with more than six years research experience after obtaining the highest degree. Time spent on non-research activities, such as medical residencies without a research component, may be excluded. **Applicants should contact Dr. Geoffrey Sunshine** (*gsunshine@healtheffects.org*, +1-617-488-2303) **if they have questions about their eligibility.**

LETTER OF INTENT

Applicants should submit a **Letter of Intent** summarizing the proposed project prior to submitting an application. The Letter of Intent (one to two pages maximum) should specify the research goals of the project and indicate the general approach to be used. The Letter of Intent should also briefly discuss the applicant's eligibility and include a Curriculum Vitae (maximum two pages). We may contact the applicant if we have questions about his/her eligibility and/or the topic of the proposal.

HEI requests Letters of Intent in order to verify the applicant's eligibility and organize the application review process, in particular to anticipate the topics of the intended proposals. If a candidate misses the deadline for Letters of Intent we urge him/her to contact HEI and submit a Letter of Intent as soon as possible after the deadline.

Deadline for Letter of Intent: A Letter of Intent should be submitted by email to *funding@healtheffects.org* (subject line: RFA 14-2 Letter of Intent) no later than **APRIL 22, 2014**, with a copy to Ms. Margarita Shablya (*mshablya@healtheffects.org*, +1-617-488-2345). HEI will acknowledge receipt of the letter.

Dr. Sunshine will contact all applicants who submit a Letter of Intent to confirm or discuss their eligibility to submit a full application.

FULL APPLICATION

Deadline for Applications: Applications for RFA 14-2 should be submitted to *funding@healtheffects.org* (subject line: RFA 14-2 Full Application) no later than **JUNE 3, 2014.** Applications should be in *PDF format* with a maximum file size of 20 MB.

After submission, please notify Ms. Margarita Shablya (see above) of your submission; do not attach the PDF documents to this second email. HEI will acknowledge receipt of the application.

Applications not meeting these conditions will not be considered.

The research proposal must be submitted on the forms **F-1 to F-12** (see list on page 33) that can be found on our website at *www.healtheffects.org/funding.htm*. Note that there is a separate set of forms for this Award; Form F-12 is optional. Investigators should consult the *Instructions for Completing the Application* found on pages 27-31. Please note that the required font size is **11 point with 1-inch margins**. Please check our website for updates. Letters of recommendation can be included with the application or be submitted to HEI directly by the referent. Please notify Dr. Sunshine which referents will be sending letters directly to HEI.

Content of Application: The full application consists of two equally important parts: (1) a formal proposal for a research project of up to three years and associated materials; and (2) evidence of the candidate's qualifications and outstanding research potential as well as a mentoring plan (see below). Inquiries regarding application and evaluation procedures may be directed to Dr. Sunshine. **Specific budget requirements:** The

project should not exceed $150,000 total costs (*i.e.*, including indirect costs) per year with a maximum of $450,000 for a 3-year project. Thus, a two-year project should not exceed $300,000 in total costs. The budget can be used to support the candidate's salary, to hire additional junior personnel (*e.g.*, postdocs, graduate or undergraduate students, or technicians), and to purchase equipment and supplies. It is expected that the investigator will devote at least 25 % of his or her time on the proposed research. Under "Other Support", please specify the candidate's time commitment to other research projects. Please contact HEI with questions about the forms.

Mentoring: Having a mentor or mentors is considered part of the supportive research environment that is required for this Award. Mentors should be active senior investigators in the area of the proposed research and be committed both to the career development of the candidate and to the direct supervision of the candidate's research. The candidate must work with the mentor(s) in preparing the application.

HEI requires candidates to submit a mentoring plan that identifies one or more senior investigators who will act as a mentor and be available for consultation during the project; it is expected that at least one of the mentors will be at the same institution as the applicant. The mentoring plan should describe in detail how and how often the mentor(s) will advise the candidate throughout the study. In addition, mentors are asked to provide a letter indicating their commitment to helping the candidate and their availability for regular consultation, as well as their research qualifications in the area of the proposed research and their experience in fostering the development of independent investigators. During the period of the Award, the mentor(s) will also be requested to provide periodic evidence — for example, in the form of a letter describing meeting dates, reviews of research plans, comments on manuscripts, etc. — that the mentoring plan is being followed. Because the Rosenblith Award is meant specifically to support the candidate's career, senior consultants can be included for percentage time but not for cost (*e.g.*, 5% effort at $0 cost). Please contact HEI with questions about how to include mentors or senior consultants on the budget pages.

Institutional commitment: HEI requires evidence of medium to long-term institutional commitment toward the applicant's career. Commitments can take many forms, such as providing laboratory space, access to core facilities, financial support for a laboratory, or paying part of the awardee's salary. In addition, it should be evident that the candidate is guaranteed at least 50% time away from teaching and/or clinical duties to pursue research and that the department includes faculty capable of productive collaboration and interaction with the candidate. If a start-up package was awarded at the time of hiring it should be described.

In addition to the materials required in the application, the following should also be submitted as evidence of the applicant's outstanding research potential:

1. A cover letter describing the candidate's interest in the award and how this project fits with his or her career goals, including information concerning the long term career plans of the applicant and how the HEI Award would contribute to these plans.

2. Two letters of reference from well-established scientists familiar with the candidate's professional capabilities but who are not directly involved in the proposed project. The letters should not focus on the scientific proposal per se, but rather address the candidate's past contributions to scientific achievements, the candidate's potential to pursue and develop an independent research program, and how the HEI Award could contribute to this potential. Whenever possible, one of these letters should be from a postdoctoral research mentor or someone else who has worked closely with the candidate. The second letter should come from an expert in the candidate's field, who is not a collaborator but can adequately judge the candidate's potential. Please note that these letters are of paramount importance.

3. One letter from the department chair, dean or other administrative official from the candidate's present institution, indicating tangible institutional commitment to the candidate and his/her research, as described above.

4. A description of the mentoring plan and letters from the candidate's mentor(s) indicating the commitment of the mentor(s) to providing consultation to the candidate on a regular basis, as described above.

5. Three recent publications and a list of all publications by the candidate.

Please refer to application form F-2-NIA (table of contents) for a list of all applications materials and the order in which they should be assembled.

RFA 14-2: EVALUATION PROCESS

Qualifications and career potential of the applicant, the quality and relevance of the proposed research, the research environment, and the mentoring plan will be considered in evaluating applications. Applications will be evaluated by HEI in the two-stage process described below:

EXTERNAL REVIEW

External scientists selected for their relevant expertise in the area of proposed research will evaluate the applications according to the following criteria:

- Scientific merit of the research design, approaches, methodology, analytical methods, and statistical procedures;
- Adequacy of the facilities;
- Appropriateness of the use of requested funds;
- Consistency of the research plan with the candidate's career goals;
- Adequacy and appropriateness of the mentoring plan.

Qualifications and research potential of the candidate will be reviewed according to the following criteria:

- Capacity to carry out independent research based on level of training, experience and competence commensurate with the purposes of this award;
- Potential to make significant contributions to the field;
- Evidence of a supportive research environment;
- Involvement of mentors or other senior consultants at the Institution or elsewhere;
- Appropriateness of the applicant's career development plan to HEI and the likelihood that the award will contribute substantially to the continued scientific development and productivity of the candidate.

INTERNAL REVIEW

The HEI Research Committee will then review the full applications and all additional materials, taking into consideration the comments and recommendations of the external reviewers. In reaching its decision, the Research Committee will evaluate not only the research proposal but also the letters of support, institutional support, and the applicant's career development and mentoring plan. The Research Committee makes final recommendations regarding the recipient(s) of the Award to the Institute's Board of Directors, which makes the final decision.

POLICY ON FOLLOW-ON APPLICATIONS

This section is addressed to HEI investigators who, when nearing completion of their projects, would like to apply to HEI for funding to continue their research. Its purpose is to describe guidelines and procedures HEI's Research Committee has adopted to evaluate requests for continuing support.

Approval of "follow-on" applications by the Research Committee will be on a highly selective basis. The Research Committee will recommend for funding only those applications most relevant to the current scientific objectives of the Institute, when evaluated against all other applications. The usual mechanism for a follow-on application involves submission of a short preliminary application. If the Research Committee is interested in the additional work, then the investigator will be asked to submit a full application for a follow-on study.

PROCESS AND TIMING FOR SUBMISSION

The Research Committee recognizes that a hiatus between projects can have an impact on experimental continuity and personnel adjustments in a laboratory. In order to minimize delay between project completion and the beginning of new research, investigators may submit a follow-on preliminary application 4-5 months prior to the contract termination date. By submitting the preliminary application during this timeframe, the Research Committee can decide whether it will be interested in reviewing a full application while the original study is still ongoing. If the Research Committee requests a subsequent full application, it can be submitted at any time after the draft final report for the original study is submitted. Although the Research Committee will begin the process for evaluating the full application as soon as it arrives, it may delay a decision until the Review Committee has completed its initial evaluation of the draft final report. Alternatively, investigators may choose to delay submission of a preliminary follow-on application until after they have submitted their final report. Please contact the assigned HEI study oversight scientist with any questions regarding the timing of submission.

PRELIMINARY APPLICATION

The preliminary application should contain two elements: a description of the project plan containing an outline of the intended procedures and techniques and a rationale for the proposed study indicating its importance in light of current insights and knowledge about air pollution and health. It is essential that the scientific questions being addressed and the specific hypotheses to be tested are explained clearly. The methodological approach to be used and innovations of significance to HEI should also be clearly described. Prior experience of the investigator(s) with the techniques to be used as well as the availability of any special equipment and facilities needed for the study should also be mentioned.

The preliminary application must be no more than five pages in length (excluding references and curricula vitae); applications longer than the page limit will not be considered. **Please use the Preliminary Application Form available at *www.healtheffects.org/funding.htm*.** The application should include (1) the application title, (2) the investigator(s) name(s) and institution(s), (3) contact information for the principal investigator (phone number and email address); and (4) the duration and budget of the proposed study. Please use 11-point font size and 1-inch margins throughout. Applications not meeting these criteria may be rejected.

In addition to the preliminary application, brief (2-page) curricula vitae of the principal investigator and co-investigators should be provided. This information is not included in the 5-page limit outlined above. Detailed budgetary information is not desired in the preliminary application, but investigators should indicate the estimated scope of the project in terms of time and money.

The preliminary application should be submitted electronically to the Staff Scientist with oversight for the initial study, with a copy to Ms. Margarita Shablya (*mshablya@healtheffects.org*). The investigator should contact the Staff Scientist about the timing of submission to ensure it can be discussed at the next Research Committee meeting.

FULL APPLICATION (IF REQUESTED)

The full application, if requested, should contain all of the elements for a full application to the Health Effects Institute as outlined in this RFA booklet, including a budget, a project plan, and any additional

submissions and should be prepared using forms F-1 to F-12 (see list on page 33) that can be found on our website at *www.healtheffects.org/funding.htm*. In the project plan, investigators should provide a brief summary of results available to date and describe the relationship between these results and the future experiments described in the proposal. Furthermore, the application should include a discussion of how anticipated results might apply to specific issues of potential health risks from exposure to air pollution.

HEI staff will contact the investigator after review of the preliminary application to let him/her know if a full application is requested. Instructions on how to submit the full application will be provided at that time.

CRITERIA FOR EVALUATION

Depending on the scope of the proposed research, follow-on applications may be subjected to outside peer-review prior to the Research Committee evaluation. The Research Committee's recommendation concerning approval of follow-on applications will depend on its appraisal of (1) the project just completed, (2) the scientific quality of the new proposal, (3) the ways the proposed research could improve the understanding of the specific problem under investigation; and (4) available funds. The Research Committee will take into account performance, productivity, scientific results, and responsiveness to HEI contract obligations during the initial project period.

HEI PROJECT NEGOTIATION, MANAGEMENT, AND INVESTIGATOR COMMITMENTS

HEI has two main goals in funding research. One is to build a coherent research program for each set of related studies addressing questions in a more comprehensive way than would be possible with independent studies. Another is to provide timely, high-quality information to its sponsors and regulatory agencies for technological and regulatory decisions. In order to accomplish these goals, HEI works in a cooperative fashion with investigators and keeps in close contact with them through such means as progress reports, workshops, and its Annual Conference. The progress reports are reviewed by the HEI Research Committee and staff, and by outside experts, if deemed necessary by the Research Committee. In addition, HEI requires a comprehensive final report at the end of each study, which undergoes an in-depth review by the HEI Review Committee and additional experts.

The purpose of this section is to provide information to prospective applicants about HEI's management of studies and about the process for review and publication of final reports from HEI-funded studies. Applicants should read this section carefully to ensure that they understand the commitments in conducting studies with HEI funding.

SCIENTIFIC NEGOTIATION OF PROJECT PLANS

The Research Committee may request modifications in the project plan or budget before making a final funding recommendation to the HEI Board of Directors. For example, the Research Committee may request deletion of parts of the proposed project that are less relevant to HEI's objectives or overlap considerably with other studies; sometimes changes in the range of exposure concentrations of pollutants are recommended to make them more representative of ambient conditions. This approach enables HEI to mold diverse investigator-designed studies into a more coherent research program and to generate data more relevant to regulatory needs. HEI staff scientists act as liaisons between the Research Committee and investigators in this scientific negotiation process. The end-product is a project plan that is acceptable to both the investigator and Research Committee.

RESEARCH AGREEMENT (CONTRACT)

Upon satisfactory negotiation of the project plan and budget, a contract for the study is negotiated with the Principal Investigator's institution. **HEI's Research Agreement is a cost-reimbursement contract rather than a grant.** Investigators should be aware that scientific and administrative contract negotiations may sometimes extend through a period of several months, which may result in changes in the scope or cost of the proposed study; therefore, certain portions of the applications may have to be updated prior to contract signing. In general, HEI requires that any significant changes in personnel, scope of work, and/or budget be reflected via submission of revised budgets, project plans, or other appropriate application materials prior to the signing of the contract. All studies should have a quality assurance / quality control plan in place. For human studies and major animal studies with expected regulatory significance, a written protocol should be approved by the appropriate institutional review boards before the study starts (see *Studies Involving Human Participants, Use of Laboratory Animals* and *Quality Assurance* below).

The contract contains a **Statement of Work**, which is an approved, brief description of work to be performed in each contract year, and the budget. The scope of the research conducted by the Investigator should be consistent with the Statement of Work. If results suggest new directions for research, however, the contract may be amended to allow changes in the Statement of Work upon written agreement between the investigator's institution and HEI.

Contracts are usually issued for one year, although HEI expects to provide support for the number of years initially approved by the Research Committee, provided work is progressing satisfactorily. The Research Agreement has been designed to maximize the integrity of the scientific process while providing needed protections and meeting applicable federal regulations. Once a contract is signed by both parties, an Abstract and Statement of Work written by the principal investigator may be distributed to the Institute's sponsors. These also will be available to members of the public who request them.

No work should be started nor should any study costs be incurred prior to signing of the contract unless explicit written authorization is provided in advance by HEI's Director of Finance and Administration.

STUDIES INVOLVING HUMAN PARTICIPANTS

As mentioned in the section *Instructions for Completing the Application, Additional Submissions*, the applicant must submit, with the application, a written assurance for compliance with the guidelines established by the Environmental Protection Agency (EPA) — as specified in EPA Regulation 40 CFR 26 (Protection of Human Subjects) available from EPA's Program in Human Research Ethics (*http://www.epa.gov/osa/phre/index.htm*) — and the guidelines by the Department of Health and Human Services (DHSS) concerning protection of human participants (see pages 30–31), on OMB form No. 0990-0263 (page F-11 of HEI application forms).

If HEI decides to fund a study involving human participants, the investigator needs to submit, before starting the study, a detailed protocol and documentation certifying that an appropriate Institutional Review Board (IRB) has reviewed and approved the proposed study in accordance with the DHHS regulations. The specific documentation that needs to be provided to HEI prior to starting the study is the following:

- The entire application to the IRB (including all supporting documentation submitted to the IRB, such as the study protocol, questionnaires, etc.);
- Statement of approval or exemption from the IRB;
- Approved informed consent document (if applicable) or a statement from the IRB that the investigator does not need to obtain informed consent.

According to EPA's rules, the EPA needs to review and approve all IRB-related documentation for all EPA-funded studies (including HEI studies) prior to the investigator starting the work. Therefore HEI will not sign a contract until it has received written approval from the EPA that the study's use of human participants complies with EPA regulations (40 CFR 26). The timely submission of the items listed above will avoid delays in the start of the study.

HEI also asks that the application to the IRB (including the informed consent document) be provided to HEI *at the time it is submitted to the IRB*. HEI may propose modifications to the informed consent document if it believes that the risks to the participants are not properly represented.

Applicants who are (a) utilizing data or samples from participants recruited for another study or (b) collecting additional samples from participants recruited for other studies, need to provide the IRB approval and informed consent document obtained for the original study and the IRB approval for the HEI study.

In addition, investigators will be asked to comply with HEI's Special Quality Assurance (QA) procedures (see below).

QUALITY ASSURANCE AND QUALITY CONTROL

It is the policy of HEI to require that appropriate quality assurance (QA) and quality control (QC) procedures are in place for all approved research projects to ensure the scientific community, our sponsors, and the public that the data are acquired under defined conditions and are reliable and traceable. There are two tiers of QA/QC procedures that HEI applies to all funded studies: general QA/QC procedures for all HEI funded studies and special QA/QC procedures for studies of regulatory significance (see below). A copy of *HEI's QA/QC Procedures for All HEI Studies* is included in Appendix C.

Under the **General QA/QC procedures (Part I),** HEI requires each funded investigator to provide a Quality Assurance Plan that describes the overall QA/QC procedures that will be implemented to ensure data quality and integrity. As detailed in Appendix the Plan should include the following six components: (1) the research protocol; (2) a list of standard operating procedures; (3) a list of qualified personnel; (4) record keeping procedures; (5) documented data processing techniques; and (6) quality control procedures for all data collected. The QA Plan should be developed and submitted to HEI at the start of the study. HEI may conduct data audits during the course of the study and/or audit the final report if there are concerns about data quality.

Special QA/QC procedures (Part II) pertain to approved research projects that may produce data of regulatory significance and include all human studies and certain animal studies. For these studies, HEI will select an outside qualified individual or team to serve as a quality assurance officer to aid in HEI's assessment of QA activities in the study. The external QA officer may conduct periodic audits to ascertain compliance with the study protocol and to examine records. The QA officer will also audit the final report of the study. He or she reports to HEI's Director of Science. The audit reports are confidential and are not released to persons not

directly involved in the management of the project. If HEI's Special QA procedures are to be applied to an approved animal study, the investigator will be informed by HEI's Staff Scientist overseeing the project.

The Principal Investigator, and his/her institution, have the primary responsibility for development and implementation of the procedures required by HEI for QA. In some cases — e.g. complex epidemiologic studies or multicenter studies — HEI may be able to provide some funds to support the investigator's time required to develop the protocol and the SOPs. In such cases, the applicant should indicate the period required for these activities and provide a separate budget.

PROGRESS REPORTS

Progress reports are one of the ways by which HEI keeps informed of the progress of the studies that it supports. Investigators are required to submit progress reports at five and ten months of the first year of the study. In subsequent years, five- and ten-month reports are requested as well. In the final year of the contract, the ten-month progress report is replaced by a comprehensive final report (pages 23–24).

The basic objective of the reports, particularly in the first year, is to indicate how much progress has been made in the development of experimental procedures, which objectives have been completed, and what problems, if any, have arisen. **The ten-month report is a combined progress report and renewal application for the next year's funding.** HEI's decision regarding renewal of the contract is based upon the information provided by the investigator in this report. The ten-month report should provide a detailed account of the experimental results obtained during the funding period, as well as a work plan (including a revised Statement of Work), and a budget for the coming year. Progress reports are reviewed by the Research Committee and by HEI's scientific staff.

Ten-month progress reports for studies funded under the Walter A. Rosenblith New Investigator Award should be accompanied by a letter from the mentor(s) reporting on the communications with the awardee and other mentoring that has taken place during the past year.

SITE VISITS

HEI may conduct site visits to the laboratories of its funded investigators during the course of their studies. The site visit team consists of members of the HEI Research Committee, HEI scientific staff, and other experts. The purpose of these visits is to evaluate the status of the project, to provide the investigator with expert technical advice, and to provide an opportunity for an exchange of ideas between the investigator and other experts in the field.

HEI ANNUAL CONFERENCE AND OTHER MEETINGS

Each year, HEI holds a conference that all principal investigators are expected to attend. The HEI Annual Conference provides an opportunity for HEI's sponsors to learn more about HEI studies, for HEI to receive feedback on its research program, and for informal interactions among investigators, Research and Review Committee members, sponsor representatives, and the HEI staff. Each investigator is asked to submit an abstract and poster. Abstracts are published in the Annual Conference booklet. In addition to discussion of HEI program areas, the Annual Conference generally includes special symposia on broader issues of current interest. Periodically, small workshops are organized for investigators working on projects in a particular research area. These meetings offer an opportunity for investigators doing related research to understand each other's research better and may open opportunities for coordination of studies or collaboration among investigators. In addition, critical gaps in HEI's program or ideas for new research may be identified. The cost for the PI attending the conference will be paid by HEI and should not be included in the budget for the proposed study.

FINAL REPORT

An important goal of HEI is to publish research reports of the highest scientific quality that will be of value to regulators, government officials, scientists, and the interested public. After the research has been completed, each HEI-funded Principal Investigator is required to prepare a comprehensive final report that describes the study and its findings. Because some of HEI's research projects are designed to provide information to be used in regulatory decisions, HEI places an emphasis on timeliness. Detailed instructions regarding the content of the final report and how to submit it are provided in the *Investigators' Guide: Preparing the Final Report*, see *www.healtheffects.org/funding.htm*.

The HEI Review Committee, which has no role in either the selection of investigators for funding or the oversight of studies, evaluates the investigator's final report. The objectives of the HEI review process are to (1) evaluate the scientific quality and significance of the research, (2) point out the strengths and limitations of the study, (3) place the study into scientific and regulatory perspective, (4) identify future research opportunities, and (5) communicate all the findings (positive and negative) to the Institute's sponsors and the public.

Each draft final report is peer-reviewed by scientists with appropriate technical expertise, including a biostatistician. A compilation of the comments of the reviewers, together with the Review Committee's initial review, is sent to the investigator, who has an opportunity to respond to these comments and, if necessary, to revise the report. At this stage, the Review Committee generally raises questions about methods, data, results and their interpretations, and conclusions drawn by the Principal Investigator. Occasionally, the Committee may request additional data analyses. After revisions are received at HEI and the Review Committee has discussed them and approved the report, the Review Committee prepares its commentary and an HEI scientific editor edits the report. The investigator is given an opportunity to respond to the commentary prior to publication and is asked to address the editor's queries. **The contractual obligation to prepare a comprehensive final report and to participate in the HEI review process distinguishes HEI from most other funding agencies.** Potential applicants should be aware of the effort associated with this responsibility and plan for it accordingly. HEI expects that the Principal Investigators and key members of the team will devote time during the last year of the study to the preparation and submission of the final report. Investigators should also be aware that report revisions and answering queries from HEI editing staff during the publication process will require additional time at a later date.

The HEI Research Reports, which consist of the investigator's final report and the Review Committee's commentary, are the principal means by which the Institute communicates results of its research and the evaluation and interpretation of those results. They are distributed to HEI's public and private sponsors, the scientific community, libraries that serve medical and scientific communities, and the general public. In addition, the HEI research reports are registered with the National Technical Information Services and the reports are indexed by bibliographic services such as PubMed. Research Reports that have been published are listed in Appendix B and are available on HEI's website, *http://pubs.healtheffects.org*.

Investigators should be prepared to submit, upon request from HEI, information underlying the final data analyses included in the report. Such information may include data sets that contain individual data as well as statistical code and output of statistical analyses with appropriate documentation. This information will be used internally at HEI and will be made available to the Review Committee to assist in their evaluation of the final report. Selected information may be included as appendices to the final report, in consultation with the investigator. Please note that this request is separate from the *Quality Assurance and Quality Control* requirements listed on page 22.

POLICY ON DATA ACCESS

Providing access to data from studies of the health effects of air pollution is an important element in ensuring scientific credibility, especially for studies used in policy debates. HEI has developed a policy to provide access to data for studies that it has funded in a manner that facilitates the review and validation of the work. The policy also protects the confidentiality of any volunteers who may have participated in the study and respects the intellectual interests of the investigators who conducted the study. A copy of the *HEI Policy on the Provision of Access to Data Underlying HEI-Funded Studies* is in Appendix D.

PUBLICATIONS

HEI encourages investigators to publish results of research conducted under HEI funding in the open scientific literature. HEI retains a nonexclusive license to publish material from work funded by HEI; it is the responsibility of the investigator and his/her institution to notify other publishers of HEI's rights. A statement acknowledging HEI support and a disclaimer must appear in all publications resulting from work funded by HEI. **Please use the disclaimer language in Article 16 of your Research Agreement with HEI**.

The Article states that investigators are free to present material derived from work conducted with HEI funding in peer-reviewed scientific journals or at meetings of established scientific organizations. Investigators are required, however, to inform HEI about the dissemination of the findings; in particular, to send HEI a copy of all **manuscripts based on all or part of the HEI-funded work at the time they are submitted to a peer-reviewed journal, and final versions upon publication.** Similarly, investigators are

also required to send **meeting abstracts at the time of submission and the final version of the poster or presentation slides.** Article 16 also states that HEI "discourages the disclosure of the results of the work performed under this Agreement outside the scientific community until after such results have undergone scientific peer review."

INSTRUCTIONS FOR COMPLETING THE APPLICATION

GENERAL INFORMATION

Applications must be submitted on the *HEI Application for Research Agreement* (forms F-1 to F-12; see list on page 33). Applications should be typed single-spaced, within the margin limitations indicated on the forms (1 inch minimum), and using a minimum font size of 11 pt. Interactive forms can be downloaded from our website at *www.healtheffects.org/funding.htm*.

Any contract awarded under this Request for Applications is expected to be funded in part by a grant from the U.S. Environmental Protection Agency. This award process will be subject to regulations contained in 40 CFR Subchapter B, and particularly Part 30 thereof. Neither the United States nor the U.S. Environmental Protection Agency is nor will be a party to this Request for Applications or to any resulting agreement.

HEI and its funded institutions are subject to the Office of Management and Budget and EPA accounting regulations.

BUDGET (FORMS F-4 AND F-5)

Cost or Pricing Data: Provide adequate data and analysis to assure HEI that the proposed costs are necessary and reasonable and that adequate accounting procedures will be used. HEI has no specific limitation on the budgets of research proposals (with the exception of the Walter A. Rosenblith New Investigator Award). Most studies funded to date have been within a range of $125,000 to $300,000 per year, including indirect costs. Projects requiring larger budgets or time periods longer than three years must have exceptional promise of developing important methods or information for understanding the health effects of automotive emissions. For applications responding to RFPA 14-1, the budget should be prepared assuming a project start date of October 1, 2014; for RFA 14-2 it should be January 1, 2015.

The total budget should include funds and an appropriate percent effort from key personnel for writing the final report in the final year of the study. Investigators should also be aware that additional time effort is expected at a later time to address requests for revisions and answering editorial queries. Please refer to the *Final Report* section on pages 23-24 for details.

PERSONNEL

List the names and positions of all applicant organization personnel involved in the project, both professional and nonprofessional, whether or not salaries are requested. Estimate the percentage of time or effort, or hours per week, on the project for professional personnel in relation to the total professional activity commitment to the applicant organization; estimate the hours per week on the project for nonprofessional personnel. List the dollar amounts separately for each individual for salary and fringe benefits. Fringe benefits may be requested to the extent that they are treated consistently by the applying organization as a direct cost to all sponsoring agencies.

The amount to be reimbursed to each individual, when added to his or her compensation for all other full-time duties, should not exceed the individual's base salary. In computing estimated salary changes, an individual's base salary represents the total authorized annual compensation that an applicant organization would be prepared to pay for a specific work period whether an individual's time is spent on sponsored research, teaching, or other activities. The base salary for the purposes of computing charges to an HEI Research Agreement excludes income that an individual may be permitted to earn outside of full-time duties to the applicant organization.

Where appropriate, indicate whether the amounts requested for the principal investigator and other professional personnel are for summer salaries or academic-year salaries and indicate the formulas for calculating summer salaries.

Indicate whether current rates or escalated rates are used. If escalation is included, state the degree (percent) and methodology, e.g., annual flat rate applied to base rate as of a specific date or a mid-point rate for the period of performance.

HEI requires the involvement of a (bio)statistician in the study design, selecting appropriate statistical approaches, and the final data analysis and interpretation. Statisticians can be included under the main study personnel or as consultants. If the investigator's Institution provides core statistical services, this should be indicated; in this case, a particular statistician should be identified by name. Exemption from this requirement can be obtained only if the Principal Investigators or other key personnel have appropriate

expertise in this area, evidence of which should be submitted as part of the application. The statistician's involvement should be evident in the application, for example by including a letter from the statistician indicating that they have read the application and approve the study design and statistical approaches. (See also *Additional Submissions* on pages 30–31).

CONSULTANT COSTS

Consultant service should be explained by indicating the specific area in which such service is to be used. Identify the contemplated consultants. State the number of days of such services estimated to be required and the consultant's quoted rate per day, and indicate the number of hours per day in which work will be performed. The maximum consultant rate is $600/8-hr day. HEI's participation in consultant costs is subject to limits set by federal regulations. (See also *Additional Submissions* on pages 30–31).

SUPPLIES AND OTHER EXPENSES

All supplies and other expenses should be itemized in sufficient detail to allow reviewers to understand the major categories of expenditures (i.e., glassware, media, chemicals, animal purchase and housing, as well as publication costs, page charges, and books, listed by category and unit cost). Itemize and justify such items as patient compensation, travel, and per diem costs, rentals, leases, and computer costs. Unusually expensive items for special processes should be separately identified by quantity and price and the use or application thoroughly explained in the project plan. Each individual expense item must be categorized as supplies or other expenses according to the practices of the accounting office of your institution. Items that cost more than $5,000 should be listed under equipment (see below).

The costs of construction per se are not permissible charges. If the costs of essential alterations of facilities, including repairs, painting, removal or installation of partitions, shielding, or air conditioning, are requested, itemize them by category and justify them fully. When applicable, indicate the square footage involved, giving the basis for the costs, such as an architect's or applicant's detailed estimate. When possible, submit a line drawing of the alterations being proposed.

TRAVEL EXPENSES

Limit travel to one scientific meeting per year. Do not include the travel to the HEI Annual Conference within the budget, since HEI will cover these costs directly. If travel is required for other purposes, such as meetings with collaborators, indicate the estimated number of trips, destination, reason for travel, and cost. Identify and support any other special transportation costs attributable to the performance of this project. HEI pays for foreign travel only if it is approved in advance of the trip.

INDIRECT COSTS

Indirect costs are limited to a maximum of 30% of direct costs excluding equipment charges and subcontracts. Indirect costs cannot be greater than the government-negotiated rate for your institution. Expenses normally included in the calculation of the indirect cost rate may not be itemized as direct expenses. Please attach a copy of your institution's most recent approved indirect cost rate. Budget review will be delayed if the indirect cost rate certification is not attached.

The HEI Board of Directors has approved a very limited exception to this cap on indirect costs for organizations that can meet both of the following conditions: (1) the research institution provides a unique capability for a project essential to HEI's mission, and (2) the institution is prohibited by the U.S. Government from accepting less than full cost recovery.

EQUIPMENT

Provide an itemization and justification of all equipment to be purchased or fabricated for use in this study. Please note that HEI reimburses institutions only for those equipment items explicitly listed in the Approved Budget or subsequently authorized in writing by HEI's Director of Science or Director of Finance & Administration. The equipment budget is not subject to indirect cost charges.

SUBCONTRACTS

Itemize and enter a total for these costs. Describe and justify all appropriate costs for services purchased for, or associated with, third parties, including applicable indirect costs. These costs may include, but are not necessarily limited to, consortium agreements or formalized collaborative agreements. Indirect costs for subcontracts are also subject to HEI's 30% cap (see above). Develop separate budgets for the initial and future budget periods for each organization involved in consortium arrangements or formalized collaborative

agreements, and submit them using the appropriate budget form (F-4b and F-5b). Subcontract budgets are not subject to indirect cost charges by the principal investigator's institution.

OTHER SUPPORT (FORM F-6)

Describe current and pending grants or contracts from which the investigators included in the proposed project are now drawing or anticipate drawing support. Identify program by title, agency, or organization supporting such work, and level of financial support given, and the percentage of time spent on each project. Briefly describe the contents of each. If any of these overlap, duplicate, or are being replaced or supplemented by the present application, justify and delineate the nature and extent of the scientific and budgetary overlaps or boundaries.

RESOURCES AND ENVIRONMENT (FORM F-7)

Describe all the facilities to be used and, in the space provided, indicate their capacities, pertinent capabilities, relative proximity and extent of availability to the project. List the most important equipment items available for this project, noting the location, and pertinent capabilities of each.

BIOGRAPHICAL SKETCHES (FORM F-8)

Provide information on the education and research and/or professional experience for professional personnel and consultants beginning with the Principal Investigator. Please do not exceed 2 pages per individual.

PROJECT PLAN (FORM F-9)

The Project Plan should include all the sections listed below. Include sufficient information in the Project Plan and in any appendix to facilitate an effective review. Be specific and informative and avoid redundancies. Sections A, B, and C together should total no more than four single-spaced pages. The Institute reserves the right not to consider proposals that exceed this limit. Appendices may be provided as supplementary information, but review will be based mainly on the information provided in the Project Plan. Section D should be concise but adequately detailed to permit critical evaluation. Section D should not exceed 15 pages (excluding references). **Please use an 11-point font size or larger and 1-inch margins**.

A. Objectives

State concisely and realistically what the research described in this application is intended to accomplish and/or what hypothesis is to be tested.

B. Anticipated Results and Significance

Briefly sketch the background to the present proposal, critically evaluate existing knowledge, and specifically identify the gaps that the project is intended to fill. State concisely the importance of the research described in this application by relating the specific aims to the stated objectives of HEI and explain the regulatory significance.

C. Related Previous Studies

Provide an account of, and references to, the principal investigator's previous studies pertinent to the application and/or any other information, including preliminary findings, that will help to establish the experience and competency of the investigator to pursue the proposed project. The appendix can be used for published references or details of available pilot studies.

D. Experimental Plan and Methods

Discuss in detail the experimental design and the procedures to be used to accomplish the specific aims of the project.

Define your study sample (such as cell type, animal strain, or subject population) and explain the rationale for choosing it. If the study involves human participants, describe how they will be selected, and the informed consent procedure. (See *Additional Submissions* below).

HEI is committed to research that can lead to a better understanding of health responses of all members of the general population, particularly the most sensitive. Accordingly, consider the composition of the study population, including gender, racial/ethnic composition, and other aspects that might affect response, and provide a rationale for the choice of composition.

Provide sufficient details of the experimental design and study protocol so that it can be understood clearly by the reviewers. Applicants should provide details of exposure systems for specific pollutants (and the rationale for their selection), randomization procedures, methods used for any blinding of observations, and the proposed number of observations (including number of animals or participants and exposure groups). Describe any new methodology and its advantage over existing methodologies.

Discuss the potential difficulties and limitations of the proposed procedures and alternative approaches to achieve the aims.

Where appropriate, describe the procedures to be used to ensure that the quality of the data is adequate in view of the objectives of the study (see *Quality Assurance and Quality Control* on page 22). However, detailed QA information should not be submitted with the original application but will be requested for successfully funded studies that meet the above criteria.

E. Statistical Design and Analysis Plans

Provide calculation of statistical power, and a justification of the proposed numbers of animals/participants/samples. Include a description of the statistical methods to be used for analysis and interpretation of the data. Describe the proposed statistical procedures with sufficient detail to allow evaluation by a biostatistical reviewer. Please note that in addition to reviews by experts in the subject matter, HEI often asks statisticians to review the statistical design of studies.

F. Literature Cited

References in the text should consist of author and year. Provide complete citations in alphabetical order at the end of the Project Plan.

ADDITIONAL SUBMISSIONS (FORM F-10)

Human Participants

If Item 6 on the Title Page (Form F-1) of the application has been marked "YES," submit OMB form No. 0990-0263 (page F-11 of HEI application forms).

Safeguarding the rights and welfare of human participants in projects supported by EPA grants is the responsibility of the institution, which receives or is accountable to EPA for the funds awarded for the support of the project. The EPA regulations require applicant institutions to comply with the Department of Health and Human Services (DHHS) guidelines for human participants as well as additional requirements specified by the EPA. HEI is responsible for ensuring that these guidelines are followed by all Institutions and investigators receiving HEI funds.

The Institution must submit to HEI, for review, approval, and official acceptance, a written assurance of its compliance with guidelines established by the Department of Health and Human Services concerning protection of human participants. However, institutions that have submitted and have had accepted general assurance to DHHS under these guidelines will be considered as being in compliance with this requirement (as documented by form F-11.) The DHHS's regulation, 45 CFR 46, is available from the Office for Protection from Research Risks, National Institutes of Health, Bethesda, MD 20892, or from the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20420, USA. Institutions outside the U.S. that have not obtained assurance of compliance to DHHS will need to provide assurance of compliance to the World Health Organization/Council for International Organizations of Medical Sciences (WHO/CIOMS), national agencies, or United Nations agencies.

If the application involves human participants, the application should include the following information on Form F-10:

- Identify the sources of the potential participants, derived materials, or data. Describe the characteristics of the participant population, such as their anticipated number, age, gender, ethnic background, and state of health. Identify the criteria for inclusion or exclusion. Explain the rationale for research involving fetuses, in vitro fertilization, pregnant women, children, institutionalized mentally disabled participants, prisoners, or other participants, especially those whose ability to give voluntary informed consent may be in question.
- Describe the recruitment and consent procedures to be followed, including the circumstances under which consent will be solicited and obtained, who will seek it, the nature of information to be provided to prospective participants, and the methods of documenting consent. Include the consent form to be used.

- Describe potential risks to the participants — physical, psychological, social, legal, or other — and assess their likelihood and seriousness. Describe alternative methods, if any, that were considered and why they will not be used.
- Describe the procedures for protecting against or minimizing potential risks and include an assessment of their likely effectiveness. Include a discussion of confidentiality safeguards, where relevant, and arrangements for providing medical treatment if needed.
- Describe and assess the potential benefits to be gained by the participants, as well as the benefits that may accrue to society in general as a result of the planned work.
- Discuss the risks in relation to the anticipated benefits to the participant and to society.

If HEI decides to fund a study involving human participants, the investigator will be asked to submit a detailed protocol before starting the study and to comply with HEI's special QA/QC procedures (see *HEI Project Negotiation, Project Management, and Investigator Commitment,* and *Appendix C*). Approval of the study by the Institutional Review Board (IRB) at the investigator's institution is required before starting a study with human participants. In addition, HEI will need to obtain approval from EPA before signing the contract, as described under *HEI Project Negotiation, Project Management, and Investigator Commitment* on pages 21–25. Documentation submitted to HEI should include (1) the complete application to the IRB; (2) consent forms, if applicable; and (3) a signed letter from the IRB indicating that the study has been approved or exempted.

Laboratory Animals The applicant shall provide with the application written assurance that any use of laboratory animals will comply with the provisions of the Animal Welfare Act (7 U.S.C. S 2131 et. seq.) and the guidelines set forth in the Guide for the Care and Use of Laboratory Animals. These documents are available from the Office for the Protection from Research Risks, National Institutes of Health, Bethesda, MD 20892. When laboratory animals are to be used in the proposed studies, state the species, strains, ages, and numbers of the animals involved and the methods to be used to comply with the above-mentioned guidelines. If approval from the Institutional Animal Care and Use Committee has been obtained, the approval letter should be included with the application. Investigators are also encouraged to read the following guidelines, *Animal Research: Reporting of In Vivo Experiments (ARRIVE) Guidelines* (see *http://www.nc3rs.org.uk/page.asp?id=1357*); although these guidelines pertain to reporting of research, HEI urges investigators to plan animal experiments being cognizant of the ARRIVE recommendations.

Recombinant DNA Applicants proposing work with recombinant DNA should adhere to the current *NIH Guidelines for Research Involving Recombinant DNA Molecules*. A copy of the Guidelines is available from the Office of Recombinant DNA Activities, National Institutes of Health, Bethesda, MD 20892.

Sponsor Participation If "YES" has been marked under sponsor participation (i.e. any of the organizations funding HEI) on page F-7 of the application form, please explain on a separate sheet the nature of sponsor participation. Identify and explain the role of any individual employed by EPA or industry sponsors of HEI (see *www.healtheffects.org/sponsors.htm*) who is involved with any aspect of the proposed study. Also, list any resources provided by sponsors, including animals, equipment, and facilities. Please note that employees of organizations funding HEI cannot receive funds from HEI for salary or any other costs.

Consultants Consultant arrangements and proposed collaborations with investigators at other institutions must be confirmed in writing. Attach appropriate letters from each individual, confirming his or her role in the project.

Statistician The assigned (bio)statistician needs to provide written confirmation that s/he (1) has reviewed and approved the study design and statistical approaches, and (2) will be actively involved in data analysis and interpretation.

Additional Materials (Rosenblith Award only) Applications to the Walter A. Rosenblith New Investigator Award should include a cover letter, two letters of reference, a letter indicating institutional support, a mentoring plan with letters form each mentor, three recent publications and a list of all publications by the candidate. Please refer to the RFA for details and use Form F-2-NIA to assemble the materials in the order requested.

Quality Assurance All applicants should provide a quality assurance plan that includes a list of standard operation procedures, qualifications of personnel, and other measures in place to assure the quality of the research and resulting data. In addition, HEI applies special QA procedures to all approved research projects that are anticipated to produce data of regulatory significance. This includes all human studies, as well as

certain designated animal studies. Those studies will undergo an external audit, and the final report will include a QA Statement from the auditor(s). See *Quality Assurance and Quality Control* on page 22 and *Appendix C* for more details.

Personal Data **(Form F-12)** HEI has a continuing commitment to monitoring the operation of its review and award process to detect, and deal appropriately with, real or imagined inequities with respect to age, ethnicity, race, or gender of the proposed principal investigator. To provide HEI with the information needed to fulfill this commitment, we request that each applicant complete the optional personal data form (Form F-12) and attach it as the last page of the signed original application. Upon receipt at the HEI office, this form will be separated from the application and used only for internal HEI monitoring procedures. **If you do not wish to provide this information, or do not complete the form, it will in no way affect consideration of your application.**

LIST OF APPLICATION FORMS

For interactive forms please visit *www.healtheffects.org/RFA/Forms/RFAforms.htm*.
Forms F-1 through F-12 are available as a combined Word file.

Preliminary Application Form

Full Application package:

F-1: Title Page
F-2: Table of Contents *or*
F-2-NIA: Table of Contents (*Rosenblith Award only*)
F-3: Abstract of Project Plan
F-4a: Budget for First 12 Month Period
F-4b: Budget for First 12 Month Period (Subcontract)*
F-5a: Budget for Total Project, and Budget Justification
F-5b: Budget for Total Project, and Budget Justification (Subcontract)*
F-6: Other Support
F-7: Resources and Environment
F-8: Biographical Sketch
F-9: Project Plan
F-10: Additional Submissions
F-11: Protection of Human Subjects
F-12: Personal Data on Principal Investigator (*optional*)

** If there is no subcontract, Forms F-4b and F-5b do not have to be submitted.*

APPENDIX A: SECTIONS OF THE HEI STRATEGIC PLAN (2010–2015)

The HEI Strategic Plan 2010–2015 describes the projected research programs and review activities for the period 2010–2015. This plan was developed with ideas and input from HEI's sponsors, the scientific community and other constituents. The detailed plan was issued in April 2010 and is available on our Web site at www.healtheffects.org/funding.htm. Below, we provide an overview of the research opportunities that are included in the Plan. Please note that most of the research outlined in the Plan is now underway. A new Strategic Plan for 2015–2020 is currently under development; please check the HEI website near the end of 2014 for updates.

PRIORITY RESEARCH OPPORTUNITIES 2010–2015

The HEI Strategic Plan 2005–2010 identified finding ways to improve the understanding of the health effects of the air pollution mixture as a top priority, and focused HEI's efforts on three key components of that mixture: PM, gases, and air toxics. This flowed quite logically from the knowledge that no one is exposed to only one pollutant and from strong recommendations at the time by two committees of the National Research Council on PM Research Needs and Air Quality Management that the nation should begin the shift from a one-pollutant-at-a-time perspective to a multipollutant perspective.

In the intervening years, the need for this broader approach has become even more compelling, with the U.S. EPA increasingly seeking to *move its programs to a multipollutant perspective*, and Europe attempting to take that perspective in setting its ambient air quality standards through the CAFE process. Yet the scientific challenges remain: designing studies that systematically investigate a range of pollutants and their potential independent, synergistic, and antagonistic effects is difficult, and made more difficult by a lack of available statistical techniques to allow consideration of the effects of more than a few pollutants at a time.

To those multipollutant challenges has been added the growing awareness of the intersection between *air quality and climate*: the potential effects of different conventional pollutants such as ozone, carbon particles and sulfate particles on climate; the effects of a changing climate on levels of conventional pollutants, such as ozone; and the need, as climate mitigation actions are designed and new technologies developed, to assess those actions for the potential health benefits (in terms of reduced air pollution and health effects) and dis-benefits (e.g., the ability of some pollutants to mitigate against climate change). While many of these issues are the subject of a much wider discussion and debate, HEI is particularly interested in their health effects implications. These issues permeate some areas of HEI research, such as those discussed in the next section and the health issues discussed later under New Fuels and Technologies.

MULTIPOLLUTANT EXPOSURE, EPIDEMIOLOGY, AND TOXICOLOGY RESEARCH

With these challenges in mind, HEI has already begun — through its NPACT initiative and its recent RFA 09-1 (seeking new statistical techniques for analysis of mixtures) — to address these important issues. Following its new Strategic Plan, HEI expects to continue to focus on the key topics of PM, the major gases (ozone, NO_2, CO, and SO_2), and air toxics, with increasing efforts to combine the study of these different pollutants for an integrated approach to the air pollution mixture, and to continue to ensure that statistical issues (such as model selection, sensitivity analysis, and confounding) are addressed in each study. We describe below a number of continuing and new opportunities for the *HEI Strategic Plan 2010–2015.*

MAJOR PROGRAMS TO BE COMPLETED

The NPACT Initiative In 2007, HEI launched this comprehensive initiative to shed light on a key issue regarding the toxicity of PM: *Are all components of PM from various sources equally toxic to health, or are some components more toxic than others?* The HEI NPACT studies combine coordinated efforts in exposure assessment using sophisticated new techniques, epidemiology focused on PM components and long-term effects, and toxicology focusing on health end points that are relevant to the health effects observed in epidemiologic studies. Two teams of investigators, led by Dr. Mort Lippmann at New York University and Dr. Sverre Vedal at the University of Washington, Seattle, are leading the studies under this initiative. The studies were published in October 2013, see *http://pubs.healtheffects.org*.

The Lippmann study has four components:

- **Subchronic animal inhalation toxicology:** Evaluating cardiovascular effects in ApoE knockout mice of 6 months of inhalation exposure to concentrated ambient fine particles at sites in the United States with different source profiles and PM composition: New York City; Sterling Forest, N.Y.; Seattle, Wash.; Irvine Calif.; and Ann Arbor, Mich.

- **Acute biologic effects of resuspended particles of different sizes:** Assessing acute biologic effects of ambient air coarse ($PM_{10-2.5}$), fine ($PM_{2.5}$), and ultrafine ($PM_{0.1}$) particles — obtained at the sites mentioned above — on epithelial cells, endothelial cells, and cardiomyocytes in vitro, and in vivo when aspirated into the lungs of mice.
- **Time-series analysis of effects of PM components:** Conducting time-series analyses of daily morbidity and mortality effects of individual fine particle components and source-related mixtures in communities throughout the United States that have fine particles of different composition.
- **Analysis of effects of PM components:** Evaluating, with a focus on longevity reduction, the effects of chronic exposure to fine particle components using information from the American Cancer Society cohort and database. The investigators will attempt to link effects to specific components and sources.

The Vedal study focuses on three areas and complements many features of the Lippmann studies:

- **Exposure:** Drawing on participants of the Multi-Ethnic Study of Atherosclerosis (MESA) cohort, the study is estimating exposure using sophisticated modeling, taking into account meteorology, traffic, land-use patterns, nearby sources, air monitoring and speciation data, temporal and spatial variation estimates, home characteristics and infiltration estimates, and time-activity data. Thus, estimates of exposure will ultimately be based on residential-level estimates of component concentrations and proximity to sources.
- **Epidemiology**: Drawing on participants of the two major cohorts (MESA–Air Pollution [a MESA ancillary study] and Women's Health Initiative–Observational Study [WHI-OS]), the epidemiologic component of the study will estimate the effects of long-term exposure to $PM_{2.5}$ components and emission sources on cardiovascular endpoints (carotid intima-media thickness and coronary artery calcification).
- **Toxicology**: The study is assessing cardiovascular effects in ApoE knockout mice (in the $ApoE^{-/-}$ mouse model) when exposed for 6 weeks to lab-generated atmospheres. Several endpoints between epidemiologic and toxicologic studies overlap. The oxidative potential of the lab-generated atmospheres and of samples collected at MESA-Air sites is also being assessed.

Statistical Methods for Analyzing the Effects of Mixtures Under an RFA issued in 2009, HEI funded three studies focused on the development of novel or enhanced statistical methods for analyzing the effects of air mixtures and then testing these methods in existing databases. Dr. John Molitor at the Imperial College, London, plans to cluster joint patterns of air pollution exposures and relate these to health outcomes. He is using recently developed Bayesian dimension-reduction and clustering techniques that will characterize the pollutant patterns contained in two datasets – the HEI RIOPA data and the Environmental Pregnancy Outcome Study from Southern California. Dr. Brent Coull of the Harvard School of Public Health adapted a class of methods, known as *model-based supervised clustering*, as an approach to assessing the joint effects of multiple air pollution constituents. This study allows both the quantification of differences in a health outcome due to different mixture profiles and the identification of the components that differentiate these mixture classes. He tested his model using epidemiologic data from the Maintenance of Balance, Independent Living, Intellect and Zest in the Elderly (MOBILIZE) study and toxicologic data collected by John Godleski (using concentrated ambient particles). Eun Sug Park, at the Texas Transportation Institute, exploited the high correlations among multiple pollutants to characterize air pollutant mixtures emitted by a few common underlying sources. To achieve this, she developed enhanced multivariate receptor models and build a coherent statistical model that can estimate health effects specific to sources of multiple air pollutants while accounting for uncertainties in unknown number of sources and estimated source-specific exposure. She tested this model in two data sets collected, respectively, in Phoenix, Ariz., and Harris County, Tex. These studies began in early 2010; two were completed during 2013 (Park and Coull) with the third expected to be completed in 2014 (Molitor).

Better Characterization of the Relationship Between Indoor, Outdoor, and Personal *Exposure* HEI published RFA 08-1 in late 2008, titled "*Relation of Indoor, Outdoor and Personal Air (RIOPA): Analysis of collected data from the RIOPA Study*." The RIOPA study determined the concentrations of VOCs, carbonyls and $PM_{2.5}$ in outdoor, indoor, and personal air for participants living in three urban areas, and HEI has ensured that the data are now well organized and publicly available at *http://riopa.aer.com.* HEI has funded two studies under RFA 08-1. In one study, Stuart Batterman of the University of Chicago used state-of-the-art statistical modeling techniques to conduct further analysis of the RIOPA database. His objective was to identify and characterize exposure distributions, exposures to pollutant mixtures, and dependencies between pollutants and determinants of exposure. The study was recently completed. In another study, Patrick Ryan of the University of Cincinnati examined the elemental composition of the RIOPA samples and determine how they vary across individuals and cities. The study is also intended to assess the impact of different factors — including time-activity patterns, housing characteristics, and home proximity to traffic and pollution point-sources — on elemental concentrations. The approaches developed in these two studies are likely to refine exposure assessments and modeling of pollutant concentrations, and may be useful in future large-scale epidemiological studies. This study will be completed in early 2014.

Completion and Publication of Air Toxics and Other Studies Initiated under Previous Plans HEI completed the research phase and published the studies on PM and air toxics that were initiated under the previous Strategic Plan. HEI published final reports, along with the Review Committee's commentaries, on the five studies characterizing atmospheric concentrations and exposures to *air toxics* in areas suspected of higher levels, or so called hot spots. HEI also published studies focused on PM and allergic response, mechanisms of toxicity of acrolein and 1,3-butadiene, and improved exposure assessment for acrolein.

MAJOR NEW OPPORTUNITIES

Effects of Ozone and PM on the Cardiovascular System The effects of ozone on the respiratory system have been studied in the past, but very little information is available on the effects of exposure to near ambient levels of ozone on the human cardiovascular system; even less is known about how such effects may be modified due to the presence of other pollutants. In early 2010, HEI issued an RFA to answer these questions in a systematic fashion. In the first phase of studies funded under this RFA, investigators are exposing human volunteers, age 55 to 70 — a group that is more susceptible to cardiovascular effects than young adults, who have frequently been studied — to ozone at near ambient levels and examine the response of the cardiovascular system (the primary endpoint), along with respiratory and inflammatory effects (the secondary endpoints). The second phase will focus on cardiovascular responses in the same subgroup of the population, but will be measured after exposures in ambient settings to ozone at concentrations similar to those studied in the laboratory but in the presence of other air pollutants — especially PM. Phase II studies will use a protocol as comparable to the controlled-exposure protocol as possible so that the results obtained in the two phases can be compared; these studies may also be performed in two or more regions of the U.S. to capture the effects of geographical variations. Investigator teams selected under this RFA have worked with HEI to develop a common protocol and standard operating procedures. As a part of this study, HEI encourages investigators to supplement established health-effects assessment methods with promising, newer methods or analytical techniques, such as those derived from genomic or proteomic research. The studies will fill important gaps in our knowledge regarding the effects of ozone and its interaction with other pollutants.

Research to Further Understand Toxicity among Air Pollutants That May Be Important Climate Change Agents HEI's NPACT initiative is systematically exploring the relative toxicity of different components of the PM mixture. One important component of ongoing research in this area will be to focus, in a multi-pollutant context, on air pollutants (such as carbon and sulfate particles, ozone, and NO_X) that can affect human health, that may be affected by changing climate (e.g., ozone), and that also may affect near-term trends in climate change. This could lead to a better understanding of which conventional pollutants should have highest priority for reduction for both air quality and climate reasons, and suggest more effective actions. It could also better inform efforts to estimate the near term health "co-benefits" of certain actions, as well as the potential "dis-benefits" of actions that might either increase some pollutants (e.g., aldehydes from biofuels), or might remove pollutants that mitigate against climate change (e.g., sulfate particles). This will not be a simple area of science; HEI would expect to organize a focused workshop, as NPACT results begin to become available, to discuss the most effective way to pursue this in an integrated, multipollutant manner.

Multipollutant Air Toxic and Other Pollutant Exposure and Health Studies in High-Exposure Situations Certain special situations and micro-environments may increase the likelihood of elevated exposures to *air toxics, criteria pollutants,* and *other pollutants such as ultrafine particles*. Although NAAQS-related controls can be expected to reduce many pollutants in such areas, a number of other less-regulated pollutants may continue to pose health concerns. In addition to offering a better understanding of the sources and other factors influencing such exposures, these situations also provide opportunities for methods development for exposure and health assessment. Examples of such situations include exposure near ports, industrial areas or major roads, dense urban areas, and certain occupational environments. HEI has previously supported several studies in locations with suspected elevated concentrations of air toxics. The five reports have now been published (by Drs. Fujita, Harrison, Lioy, Smith, and Spengler). Based on knowledge gained from that experience, HEI will work to identify and implement multipollutant studies of exposure and health in well-documented high-exposure situations. Additionally, short-term peak exposures in certain situations can be high and may be masked by time-averaging; HEI will also seek opportunities for research in situations where the short-term concentrations are elevated.

Filling Key Gaps Identified in HEI's Review of Traffic-Related Air Pollution The recently published HEI review, Special Report 17, *Traffic-Related Air Pollution: A Critical Review of the Literature on Emissions, Exposure, and Health Effects* (HEI 2010), has highlighted the importance of filling key gaps in research on exposure and the health of people living in proximity to major roads. The traffic review also highlighted the scientific need to understand the atmospheric transformations and dispersion of tailpipe emissions of air toxics and other pollutants, as well as the spatial and temporal patterns of such pollutants. The review also highlighted the impact of land use patterns and traffic patterns on pollutant exposure. Given the number of people who live in close proximity to major roads — with potential long-term exposures

and health effects — the HEI Research Committee has worked with sponsors and others to identify top-priority needs from this review and implement programs to meet those needs. Such studies may include:

- One or more areas of atmospheric chemistry and transformation of primary mobile-source pollutants;
- Enhanced investigation of the role of traffic exposure in premature mortality and other endpoints;
- The relative role of other sources — including stationary sources, break and tire wear, fugitive dust, and others — in such effects; and
- The possibility of identifying unique "markers" for such exposures.

. HEI issued RFA 13-1 to address these issues and has selected five studies for funding that are expected to start in early 2014.

A Review of Emissions, Exposure, and Health Effects from Ultrafine Particles HEI has supported a large number of studies on ultrafine emissions and health (both toxicologic and epidemiologic). The continuing interest in ultrafine particle emissions, especially from new engine technologies and fuels, and their potential health effects suggest that a comprehensive review of this area has merit. HEI has worked with its scientific committees to launch an HEI Perspective to synthesize the state of knowledge regarding ultrafines and automobile emissions – including factors influencing ultrafine particle emissions, atmospheric transformations, variations in physical and chemical characteristics, the potential for health effects, and the remaining gaps in knowledge. HEI Perspective 3 was published in January 2013).

EMERGING TECHNOLOGIES AND FUELS

HEI has since its inception played a role in assessing new fuels and technologies; topics have included diesel exhaust, particulate traps, cerium, ethanol, methanol, the fuel additive methyl tertiary butyl ether, and manganese. At this point, however, the variety of new fuels and technologies is expanding at an unprecedented rate. Interest in such developments is high, especially given their implications for climate change, as well as conventional pollutant emission reductions. Of special interest would be early identification of any additional emissions from emerging fuels and technologies that, while enhancing fuel efficiency and reducing climate emissions, might at the same time cause increases in other pollutants. In addition, in response to various legislative and regulatory initiatives, there is a growing emphasis on understanding the new fuels and technologies from a full life-cycle perspective (from resource extraction and production through combustion and disposal). Thus, HEI expects that issues surrounding emerging technologies and fuels will occupy a larger portion of its research and review portfolio.

COMPLETION OF ACES

Phase 3 of HEI's ACES program, which includes a chronic bioassay, has been completed, and a variety of endpoints were assessed, including neoplastic changes, organ toxicity, pulmonary inflammation, oxidative damage and cell proliferation in respiratory tract tissue, mutagenicity, and cardiovascular endpoints in both rats and mice. Chronic toxicity, including carcinogenicity, were evaluated only in rats. Rats also underwent pulmonary function testing. Some of these studies were done under separate contracts with investigators who have expertise in these areas; the exposure group at LRRI provided the samples for testing. The final reports of ACES are currently under intensive peer-review by the HEI Review Committee and are expected to be published in 2014. In addition, Phase 2, the emissions characterization of and ultimate health effects testing for 2010 engines, was completed and published in 2013.

REINVIGORATION OF THE SPECIAL COMMITTEE ON EMERGING TECHNOLOGIES

The reconvened SCET will help HEI meet its research-planning goals by surveying and evaluating fuels and technologies, preparing critical summaries of scientific information on them, and identifying particularly important emissions and health effects research issues for HEI and others. This interdisciplinary group of experts is knowledgeable about future trends in automotive engineering and transportation issues, alternative fuels, aftertreatment technologies, health, and other issues.

The newly convened SCET met for the first time at the end of April 2009 and subsequently produced a report (published in 2011) that provides a brief overview of selected areas of emerging technologies and fuels, the technologies likely to stay in the marketplace, the state of knowledge about their emissions and potential health effects, and any other topics ripe for further investigation.

Based on the recommendations of SCET, HEI will identify top priority new, targeted research, as well as timely review and synthesis of information, from among the following potential areas:

- **Emissions from ethanol and other alternative fuels**. There is strong interest, in the U.S. and worldwide, in increasing the use of ethanol and other alcohols, ethers, biodiesel, compressed natural gas, and other fuels for transportation. Interest in alternative fuels has also been heightened because of legislative mandates in several

countries, including the United States, nationally and at the state level. Frequently, such fuels are blended with gasoline or diesel. However, there is a paucity of information about the emissions from the use of such fuels. Therefore, there is a need for studies focused on the characterization of the emissions from such fuels, and possibly on human exposure to the emissions and potential health effects. The introduction of such fuels may also provide opportunities for accountability research.

- **Evaluation of NO_X aftertreatment technologies for advanced diesel engines**. The possible emissions and health effects of aftertreatment technologies deployed to reduce oxides of nitrogen (NO_X) from the emissions of advanced diesel engines, such as selective catalytic reduction (SCR) or NO_X adsorbers, need further discussion and review. For example, SCR technology uses urea to remove NO_X; questions have been raised about the emission of by-products such as nitroalkanes, nitro-polycyclic aromatic hydrocarbons, and aldehydes, many of which are of potential health concern.
- **Gasoline direct injection engines:** To improve the fuel-efficiency of gasoline vehicles, auto manufacturers are increasingly and rapidly adopting gasoline direct injection (GCI). However, GDI is known to increase the emission of ultrafine PM. Since it appears likely that GDI will be used on a fairly wide scale in the near future, it is important to gain a better understanding of the exposure to and potential health effects from such emissions.
- **Electric and hybrid vehicles.** Electric and hybrid vehicles are entering the marketplace at an accelerating pace and, as in the case of alternative fuels, it seems very likely that they will occupy a greater portion of the automotive fleet in the future.. Though the tailpipe emissions from such cars are reduced or eliminated, there are other potential health effects to consider. These include (1) use of highly reactive metals – especially lithium – in the battery and the potential for human exposure to lithium during its entire life cycle (from mining to recycling and disposal); (2) whether there are health effects associated with exposure to electric and magnetic fields during the operation of the vehicles, especially as the proportion of consumers using electric and hybrid vehicles increases; and (3) potential effects of emissions associated with electricity generation. If electricity is generated from renewable sources, this is not an issue. But, in the near term, a large proportion of it will continue to be produced by coal-fired power plants, thus "dislocating" emissions from the tailpipe to the power plants. Fuel-cell vehicles appear likely to arrive in the marketplace five to ten years from now, and this will be an area of continuing monitoring by SCET.
- **Non-tail pipe emissions**. As the emissions of PM from automobile tailpipes continue to decline (at least in the industrialized countries), other non-tail pipe sources of PM in ambient air will gain more relative importance. Sources of such PM include dust from tire wear and brake linings and fugitive dust. In particular, brake and tire dust often contains metals. The issues arising from such emissions need to be better understood.
- **Studies of metals in fuel additives**. The potential of bioaccumulation of platinum, manganese, and other elements from mobile sources, and their potential toxicity are also areas of concern. Ferrocene, an iron-containing compound that may be added to diesel fuel, is of possible interest depending on the extent of its future use. Manganese is used or is being considered for use in some parts of the world as a gasoline additive as part of methylcyclo-pentadienyl manganese tricarbonyl. Metal additives are frequently emitted as metal-containing ultrafine particles. This area needs further scrutiny and research.
- **Life-cycle issues.** A cross-cutting issue for the use of any technology is its overall impact on humans and the environment throughout its life cycle (from resource extraction and production through combustion and disposal). For example, as discussed above, although electric cars produce no emissions on the street, the power plant — the source of electricity — may well produce emissions. Thus, a close look at the life-cycle issues associated with some of the new technologies – with special focus on their implications for health effects – may be warranted. Life-cycle analyses are of interest from the perspective of many disciplines, such as economics, ecology, and resource management; however, in keeping with its core expertise, HEI will focus primarily on the impact on health effects of any life-cycle factors (for example, health issues associated with the widespread use of metal-ion batteries to power electric and hybrid vehicles).

Based on SCET's review, HEI and its Research Committee – after consultations with its sponsors – will identify from among these topics the top priorities for the following:

- Timely reviews and/or workshops to get a comprehensive perspective of the state of knowledge – what is known about emissions, their chemistry, atmospheric fate, and exposure and potential health effects (see below under "*Synthesis of Information on Important Issues*"); and,
- Targeted research to fill key gaps going forward (for example, see some of the ideas discussed below under "*Innovations and Validation*").

HEI assesses new technologies and fuels, and any potential concerns regarding their impact on health, on an ongoing basis. Appropriate areas for further attention will be included in the next Strategic Plan 2015–2020.

ACCOUNTABILITY

HEI will maintain a leadership position in accountability, further defining concepts and methods and initiating the next stage of new research in this challenging field. Having completed a first wave of accountability research, HEI is building on the lessons learned from those studies through critical review, publications, and collaborative efforts to identify and exploit new data sources (e.g., environmental public health tracking). In December 2009, HEI conducted a workshop to discuss and evaluate more fully the studies supported during the first phase of HEI's Accountability program and to identify the challenges as well as opportunities and strategies for further research. The workshop focused on questions such as

- What are the lessons learned from the challenges faced in the conduct of previous studies, and how may these lessons be incorporated in the design of new studies?
- To what extent can additional studies of short-term actions deepen our knowledge about the accountability of air pollution controls?
- What opportunities are available for conducting longer-term studies, and what are the best ways for developing novel approaches to detect changes in health outcomes over the longer term?
- How can we stay abreast of policy development at the local, regional, national, and international levels to identify future needs and opportunities?
- What data sources and methods are best suited for these studies?

The detailed recommendations of the workshop were published in HEI Communication 15 (2010); among the major findings were the following:

- Further accountability research is needed, especially of long-term, national-scale interventions. This will be facilitated by the development of publicly available platforms for key research data, and will improve the ability to account for other concurrent changes that affect health over the same time frame.
- There is a cross-cutting need for determining if there is "sufficient" exposure-contrast before initiating a study.
- Research on shorter-term and small-scale actions remains useful under well-defined circumstances, and may provide supportive evidence for causal relationships if there is sufficient study power.
- We will need an enhanced and targeted method for reviewing upcoming regulatory activities and for screening them to identify the best opportunities for future studies.
- Improvements in monitoring, air quality modeling, and health tracking, together with experience gained from previous studies will provide opportunities for high-quality, "second-wave" research.

One important finding is that it would be particularly useful to incorporate accountability research as a fundamental aspect of the design and implementation of policy interventions, particularly of major regulatory programs, which occur over longer periods of time. Although targeted opportunistic approaches could still be useful, HEI will also pursue more systematic development of a body of evidence in specific areas of regulation and intervention, including some of the following:

- The impacts of introduction of new fuels and technologies over time, (e.g., biofuels);
- The impacts of a series of actions taken over the longer term designed to either reduce emissions from a particular large source (e.g., power plants) or reduce area-wide exposure to a particular pollutant (e.g., implementation of a metropolitan-area implementation plan for ozone);
- The effects of regulatory interventions on populations with exposures to multiple sources in areas with higher levels of pollution (e.g., ports and urban "hot spots");
- Systematic efforts to assess measures aimed at reducing exposure of sensitive populations; and
- Interventions designed to improve air quality significantly for major events (such as Olympic Games), especially when those actions are likely to be sustainable.

There is also a continuing need, and opportunity, to improve personal bio-monitoring programs that may be able to track reductions in personal exposure over time as a result of interventions (e.g., the ability of the National Health and Nutrition Examination Survey program by the CDC to track reductions in cotinine — a well-validated marker of exposure to secondhand tobacco smoke — as efforts to reduce exposure to passive smoke have been implemented).

To effectively carry out the next generation of accountability research, and consistent with other areas of the Strategic Plan, HEI will work with agencies to strengthen its ability to track and take advantage of upcoming regulatory interventions in the United States, Europe and other areas where the actions would be relevant to the United States.

Overall, the next generation of accountability studies will build on but also extend beyond opportunistic studies of shorter-term interventions to address larger regulatory programs implemented over longer periods of time. To do this HEI will pursue new or enhanced analytic methods, data from health tracking systems (in partnership with states and others), and the more systematic linkage of accountability studies to the adoption of major new regulatory initiatives. HEI issued RFA 11-1 in this area in 2011 and has funded four studies that are currently underway (by Drs. Gilliland, Meng, Russell, and Zigler).

AN INTERNATIONAL PERSPECTIVE

Looking ahead, HEI will build on the key themes of multipollutant approaches and research at the air quality–climate nexus as it funds the best research proposals, competitively selected from among the leading scientists in the world. This will enable HEI to take advantage of unique geographic, population and technical opportunities to fund research that informs decisions in North America, Europe, and Japan. With added support from foundations, international sponsors, and in partnership with the European Union and others, HEI will also selectively enhance its current program of research in the developing vehicle and energy markets of Asia and Latin America in order to inform decisions there and in other parts of the developing world in a manner that encourages globally relevant research results.

In some cases, as noted earlier, HEI will continue to inform decisions taken in the developed-world by seeking to

- Target HEI research to projected U.S., E.U., and other international policy trends and timelines, in the process strengthening bridges among HEI and international policy makers to enhance integration of HEI science into key science decision documents;
- Conduct accountability studies of air quality regulations and other interventions in worldwide locations that can produce results relevant in North America, Europe, and Japan;
- Implement studies of long-term exposure to air pollution and health from multiple pollutants (e.g., similar to the Netherlands study completed recently [Brunekreef et al. 2009]).
- Participate in key science oversight and evaluation groups for highly relevant studies (e.g., the European Study of Cohorts for Air Pollution Effects (ESCAPE) study of long-term effects of air pollution, *Global Burden of Disease* updates, and periodic efforts to inform health impact assessment);
- Develop new capabilities to inform decisions at the intersection of air pollution and climate emissions; and
- Support synthetic research and review in a global context through coordinated assessments of research across multiple continents.

DEVELOPING COUNTRIES AND EMERGING MARKETS

The developing countries in Asia, and to a lesser extent Latin America, are areas where — with additional support from foundations, development banks, industry, governments, and others — HEI can help accelerate the transition to science-based decision making both for traditional air pollutants and at the intersection of air pollution and climate. This approach, accomplished by leveraging existing HEI science capabilities, will also help accelerate the transition to improved public health and more globally consistent regulatory approaches. These developing countries are the world's most active future markets for new vehicles and fuels and are sources of internationally transported air pollutants and GHGs. With the significant local impacts of air pollution on health, these areas will benefit from high-quality independent science to directly inform health and regulatory decisions by national governments.

HEI, with its internationally distributed research portfolio, PAPA-SAN database, and other research tracking capabilities, as well as its regular interaction with WHO, leading scientists, research institutions, and government experts, is uniquely positioned to selectively review and synthesize regional studies in a global context. This approach, undertaken judiciously (e.g., the APHENA study [Katsouyanni et al. 2009] and the meta-analysis of Asian time-series studies currently being conducted by HEI), will enable progress toward a more synthetic understanding of key differences and similarities among developing- and developed-world populations and inform related policy decisions. New partnerships with potential sponsors in rapidly developing economies such as India and China are expected to help facilitate these efforts.

In these regions HEI will

- Publish all studies and reviews initiated under the previous Plan.
- Maintain selected PAPA activities, including
  - The PAPA-SAN database of Asian health studies as a key resource;

  - Periodic review and synthesis of the Asian scientific literature in a global context; and
  - Targeted capacity building and support for Asian scientists to provide the highest quality research for Asian policy decisions;
- Selectively undertake new studies including
  - Investigating the potential relation between exposure to air pollution and children's health (e.g., acute lower respiratory infections) as well as reproductive or developmental health effects (including two studies funded under RFA 09-2, "Impact of Air Pollution on Infant and Children's Health in Asia" by Drs. Lee and Qian);
  - Pursuing studies at the intersection of air quality, climate and health; and
  - Conducting studies of the long-term effects in existing cohorts, if technically feasible and if new external funds or funding partnerships are identified;
- Strengthen HEI's ability to synthesize and independently communicate the results of its research to government, industry, development agencies, and other stakeholders.

Taken together, these activities will maintain HEI as a domestically and globally relevant provider of independent science, regularly called to credibly inform key decisions affecting public health and potential regulation in key forums in the developed and developing worlds (with decisions in the latter arena potentially having both local impact and broader impact on developed countries [e.g., through transport to Japan and the United States from Asia]).

ISSUES THAT CUT ACROSS ALL OF HEI'S WORK

In reviewing the specific issues that HEI might address going forward, a number of specific health effects questions emerged that would not by themselves be programs of research in the new Strategic Plan, but which should be viewed as *cross-cutting issues* that should be integrated into all of HEI's work:

SENSITIVE POPULATIONS

The Clean Air Act specifically calls for protection of sensitive or susceptible populations. Based on previous health studies, it appears clear that certain groups in the population are, or may be, particularly sensitive to health effects of air pollution. Such groups include the fetus and children who are in active developmental stages; the elderly who may suffer from multiple illnesses; those with asthma, diabetes, obesity, cardiovascular, and other diseases whose underlying pathophysiology makes them more susceptible; and those who are of lower SES and thus may face higher exposures and have underlying health vulnerabilities. Also, in some situations, specific gene-environment interactions may confer susceptibility to individuals who are otherwise resistant to the effects of environmental agents. HEI will integrate such cross-cutting issues into its future research. More specifically, HEI may focus its projects on one or more susceptible groups or explore the role of genetic and epigenetic factors influencing health outcomes by utilizing techniques borrowed from genomics, proteomics, and other new biological tools.

INNOVATION AND VALIDATION

HEI has done much to advance innovative techniques for improved exposure assessment, statistical analysis, toxicology, and data access under its current Plan. In each of these areas HEI has played two key roles: to *develop innovative methods*, and then to *test and validate those methods* to ensure that they provide high-quality information for better understanding and decision making. Looking forward, there are several key opportunities for incorporating innovation and validation in all aspects of HEI's work, including

- *Enhanced statistical techniques:* In its new Plan, HEI will continue its decade-long success at identifying, developing and validating innovative statistical techniques for analyzing the relationship between air pollution and health. In addition to implementing the studies resulting from its RFA seeking novel statistical methods to address the mixture (described above), HEI will continue to identify opportunities in all of its studies to develop and test new statistical approaches, especially continuing efforts to test and explain the challenges of model selection for the interpretation of results.
- *New methods for toxicity testing*: HEI will also encourage in its research programs the use of new methods, model systems, and systems biologic approaches for toxicity testing, with the goal of improving exposure- and dose-to-target tissue assessment, genetic or epigenetic factors affecting susceptibility, and species specificity. HEI is also interested in studies focused on mechanisms of action, especially as they pertain to enhancing our understanding of species- or dose-related extrapolation or early markers of pathological outcomes. Although many others at the EPA, National Institutes of Health, and elsewhere are developing such techniques, HEI will use its unique position to apply and test these techniques in challenging areas. In view of the increasing deployment of new fuels and technologies

and the paucity of information about the health effects of their emissions, such methods will be particularly useful in the development of more reliable and cost-effective screening tools.

- *New biomarkers:* Although scientists have searched for biomarkers for a long time, advances in proteomics, genomics, systems biology, immunology, neurobiology, understanding of gene-environment interactions, and advances in various measurement methods raise anew the possibility that biomarkers may be found for certain pollutants, and these advances have the promise of providing more reliable methods for dose or exposure assessment and early markers of disease. HEI will encourage the investigators it supports to propose such approaches in their research, ideally side by side with more traditional and well-validated approaches, to build a broader "tool box," especially for assessing exposure or health effects.
- *Enhanced public access to data*: HEI has been a pioneer in making the data from its studies available to other investigators and online. In its new Plan, HEI will continue to facilitate and implement new databases to join those it has already implemented.

SYNTHESIS OF INFORMATION ON IMPORTANT ISSUES

Using special expert panels and its scientific committees, HEI has long played an important role in collecting, analyzing and synthesizing scientific information on important issues facing the EPA and its private sector sponsors. This has taken the form of both Special Reports developed by special expert panels and *HEI Perspectives* developed by the HEI Review Committee and scientific staff. Examples of such activities include reports on exposure and health effects of oxygenates (HEI 1997) and cerium (HEI 2001) as fuel additives and of MSATs (HEI 2007), and major reanalysis projects such as the Particle Epidemiology Reanalysis Project of the American Cancer Society and Harvard Six Cities Studies (HEI 2000). Very recently, HEI has published a major review of the health effects of exposure to traffic-related air pollution (HEI 2010).

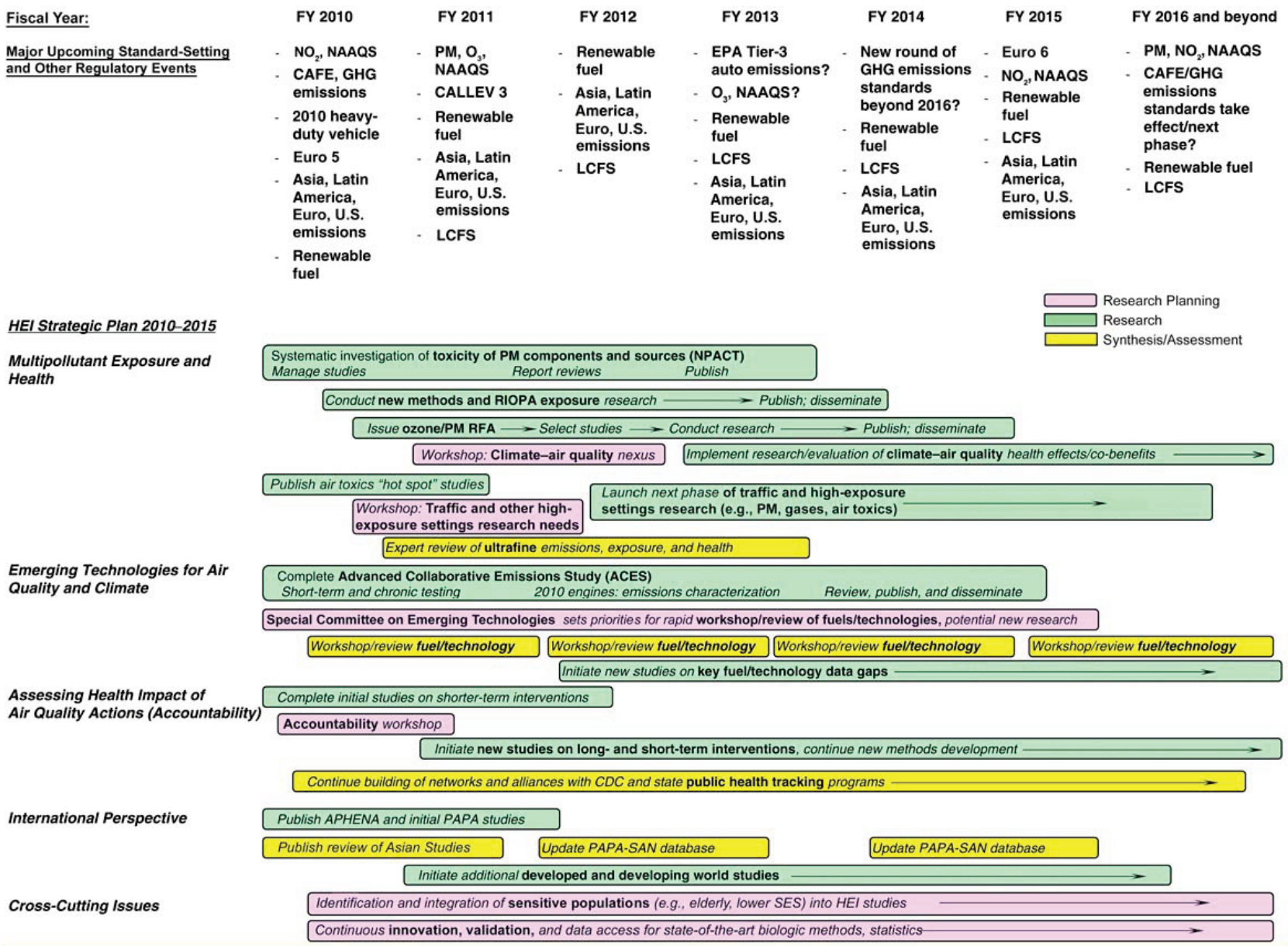
In going forward, HEI expects to continue such activities; two such types of reviews are at the top of HEI's priority list for the coming five years:

- Potential multiple-targeted assessments of health effects considerations related to the introduction of new fuels and technologies (e.g., the rapidly increasing introduction of biofuels; see section on Emerging Technologies above); and
- Exposure to and health effects of ultrafine particles. (HEI Perspective 3, focused on ultrafine PM, was published in January 2013).

IMPLEMENTING THE HEI STRATEGIC PLAN 2010–2015

Based on extensive comments from HEI sponsors, other stakeholders, and the scientific community — and the priority opportunities identified above — HEI has identified the following specific activities and timeline for implementing the HEI Strategic Plan 2010–2015 by *applying next-generation multipollutant approaches to conventional pollutants…and at the air quality–climate nexus.* Assuming adequate resources are available, these specific actions are identified in the timeline in the Figure on page 44.

[For Appendix A references please refer to the published Strategic Plan 2010–2015 on the HEI website.]


Fiscal Year:
FY 2010
FY 2011
FY 2012
FY 2013
FY 2014
FY 2015
FY 2016 and beyond
Major Upcoming Standard-Setting and Other Regulatory Events
- NO2, NAAQS
- CAFE, GHG emissions
- 2010 heavy-duty vehicle
- Euro 5
- Asia, Latin America, Euro, U.S. emissions
- Renewable fuel
- PM, O3, NAAQS
- CALLEV 3
- Renewable fuel
- Asia, Latin America, Euro, U.S. emissions
- LCFS
- Renewable fuel
- Asia, Latin America, Euro, U.S. emissions
- LCFS
- EPA Tier-3 auto emissions?
- O3, NAAQS?
- Renewable fuel
- LCFS
- Asia, Latin America, Euro, U.S. emissions
- New round of GHG emissions standards beyond 2016?
- Renewable fuel
- LCFS
- Asia, Latin America, Euro, U.S. emissions
- Euro 6
- NO2, NAAQS
- Renewable fuel
- LCFS
- Asia, Latin America, Euro, U.S. emissions
- PM, NO2, NAAQS
- CAFE/GHG emissions standards take effect/next phase?
- Renewable fuel
- LCFS
Research Planning
Research
Synthesis/Assessment
HEI Strategic Plan 2010–2015
Multipollutant Exposure and Health
Systematic investigation of toxicity of PM components and sources (NPACT)
Manage studies
Report reviews
Publish
Conduct new methods and RIOPA exposure research
Publish; disseminate
Issue ozone/PM RFA
Select studies
Conduct research
Publish; disseminate
Workshop: Climate–air quality nexus
Implement research/evaluation of climate–air quality health effects/co-benefits
Publish air toxics "hot spot" studies
Launch next phase of traffic and high-exposure settings research (e.g., PM, gases, air toxics)
Workshop: Traffic and other high-exposure settings research needs
Expert review of ultrafine emissions, exposure, and health
Emerging Technologies for Air Quality and Climate
Complete Advanced Collaborative Emissions Study (ACES)
Short-term and chronic testing
2010 engines: emissions characterization
Review, publish, and disseminate
Special Committee on Emerging Technologies sets priorities for rapid workshop/review of fuels/technologies, potential new research
Workshop/review fuel/technology
Workshop/review fuel/technology
Workshop/review fuel/technology
Workshop/review fuel/technology
Initiate new studies on key fuel/technology data gaps
Assessing Health Impact of Air Quality Actions (Accountability)
Complete initial studies on shorter-term interventions
Accountability workshop
Initiate new studies on long- and short-term interventions, continue new methods development
Continue building of networks and alliances with CDC and state public health tracking programs
International Perspective
Publish APHENA and initial PAPA studies
Publish review of Asian Studies
Update PAPA-SAN database
Update PAPA-SAN database
Initiate additional developed and developing world studies
Cross-Cutting Issues
Identification and integration of sensitive populations (e.g., elderly, lower SES) into HEI studies
Continuous innovation, validation, and data access for state-of-the-art biologic methods, statistics

APPENDIX B: HEI STUDIES AND RESEARCH REPORTS FROM 2002-2013

RFA 13-2: WALTER A. ROSENBLITH NEW INVESTIGATOR AWARD
Sally Ng, Georgia Institute of Technology
Composition and oxidative properties of particulate matter mixtures: effects of particle phase state, acidity, and transition metals (under negotiation)

RFA 13-1: IMPROVING ASSESSMENT OF NEAR-ROAD EXPOSURE TO TRAFFIC RELATED POLLUTION
Benjamin Barratt, King's College London
The Hong Kong D3D study: A dynamic three-dimensional exposure model for Hong Kong (under negotiation)
Stuart Batterman, University of Michigan
Enhancing models and measurements of traffic-related air pollutants for health studies using Bayesian melding (2016)
Christopher Frey, North Carolina State University
Characterizing the determinants of vehicle traffic emissions exposure: measurement and modeling of land-use, traffic, transformation and transport (under negotiation)
Jeremy Sarnat, Emory University
Developing multipollutant exposure indicators of traffic pollution: the dorm room inhalation to vehicle emissions (DRIVE) study (under negotiation)
Edmund Seto, University of Washington
Evaluation of alternative sensor-based exposure assessment methods (under negotiation)

RFA 11-2: WALTER A. ROSENBLITH NEW INVESTIGATOR AWARD
Jason Surratt, University of North Carolina–Chapel Hill
Understanding the health effects of isoprene-derived particulate matter enhanced by anthropogenic pollutants. (2016)

RFA 11-1: HEALTH OUTCOMES RESEARCH – ASSESSING THE HEALTH OUTCOMES OF AIR QUALITY ACTIONS
Frank Gilliland, University of Southern California
The effects of policy-driven air quality improvements on children's respiratory health. (2014)
Ying-Ying Meng, University of California, Los Angeles
Improvements in air quality and health outcomes among California Medicaid enrollees due to goods movements**.** (2014)
Armistead Russell, Georgia Institute of Technology
Impacts of emission changes on air quality and acute health effects in the Southeast, 1993-2012. (2016)
Corwin Zigler and Francesca Dominici, Harvard School of Public Health
Causal inference methods for estimating long term health effects of air quality regulations. (2015)

RFPA 10-3:
Alison Fryer, Oregon Health and Science University
Air pollution and systemic inflammation of autonomic nerves. (2014)
David Rich, University of Rochester and **Annette Peters,** Helmholtz Center Munich, Germany
Ambient and controlled particle exposures as triggers for acute ECG changes, and the role of antioxidant status. (2014)
William Kraus, Duke University
Air quality by genomics interactions in a cardiovascular disease cohort (Study under negotiation)

RFA 10-2: WALTER A. ROSENBLITH NEW INVESTIGATOR AWARD
Juana Maria Delgado-Saborit, University of Birmingham, UK
Use of real-time sensors to assess misclassification and to identify main sources contributing to peak and chronic exposures. (2015)
Richard Peltier, University of Massachusetts, Amherst
Development of a new method for measurements of reactive oxygen species associated with $PM_{2.5}$ exposure. (2014)

RFA 10-1: CARDIOVASCULAR EFFECTS OF EXPOSURE TO LOW LEVELS OF OZONE IN THE PRESENCE OR ABSENCE OF OTHER AMBIENT POLLUTANTS
John Balmes, University of California, San Francisco
Multicenter ozone study in elderly subjects (MOSES). (2015)
Philip Bromberg, University of North Carolina, Chapel Hill
Multicenter ozone study in elderly subjects (MOSES). (2015)
Mark Frampton, University of Rochester
Multicenter ozone study in elderly subjects (MOSES). (2015)
Ann Stoddard, New England Research Institute
Data analysis for the multicenter ozone study. (2015)

RFPA 09-5: HEALTH EFFECTS OF AIR POLLUTION
Gunnar Boysen, University of Arkansas
Profiling doses of reactive compounds derived from various air pollutant exposures. (Completed)

Myoseon Jang, University of Florida
Pilot study: A Novel Exposure Method to Evaluate the Health Effects of Combustion Particulate Matter. (Unpublished Report)
Fern Tablin, University of California
Immune effects of episodic ozone and PM exposure during postnatal development. (2014)

RFA 09-4: WALTER A. ROSENBLITH NEW INVESTIGATOR AWARD
Jun Wu, University of California at Irvine
Adverse reproductive health outcomes and exposure to gaseous and particulate matter air pollution in pregnant women. (2014)

RFIQ 09-3: STUDIES OF LONG-TERM EXPOSURE TO AIR POLLUTION AND CHRONIC CARDIO-VASCULAR AND RESPIRATORY DISEASE IN ASIA
No studies funded

RFA 09-2: IMPACT OF AIR POLLUTION ON INFANT AND CHILDREN'S HEALTH IN ASIA
Yungling Leo Lee, National Taiwan University
Impact of outdoor air pollution of infant and children's health in Taiwan. (Completed)
Zhengmin Qian, Saint Louis University
Air pollution and adverse pregnancy outcomes in Wuhan, China. (2014)

RFA 09-1: METHODS TO INVESTIGATE THE EFFECTS OF MULTIPLE AIR POLLUTION CONSTITUENTS
Brent Coull, Harvard School of Public Health
Statistical learning methods for the effects of multiple air pollution constituents. (Completed)
John Molitor, Oregon State University
Modeling of multi-pollutant profiles with applications of RIOPA study data and to indicators of adverse birth outcomes using data from the UCLA Environment and Pregnancy Outcome Study (EPOS). (2014)
Eug-Sun Park, Texas A & M University
Development of enhanced statistical methods for assessing health effects associated with an unknown number of major sources of multiple air pollutants. (Completed)

RFA 08-2: WALTER A. ROSENBLITH NEW INVESTIGATOR AWARD
No studies funded

RFA 08-1: RELATIONSHIP OF INDOOR, OUTDOOR AND PERSONAL AIR (RIOPA): FURTHER ANALYSES OF THE RIOPA STUDY DATA
Stuart Batterman, University of Michigan
Relationship of indoor, outdoor and personal air (RIOPA): Further analyses of the RIOPA study data. (Completed)

Patrick Ryan, University of Cincinnati
Analysis of personal and home characteristics associated with the elemental composition of $PM_{2.5}$ in indoor, outdoor and personal air in the RIOPA study. (2014)

RFA 07-1: WALTER A. ROSENBLITH NEW INVESTIGATOR AWARD
Thomas Barker, Georgia Institute of Technology
Extracellular matrix stiffness associated with pulmonary fibrosis sensitizes alveolar epithelial cells. (Completed)
Jiu-Chiuan Chen, University of Southern California
Particulate air pollutants, risk of cognitive disorders, and neuropathology in the elderly. (2015)

RFP 2007: DEVELOPMENT OF A WEB-ACCESSIBLE RELATIONAL DATABASE FOR AIR TOXICS AND $PM_{2.5}$ BASED ON THE RIOPA STUDY
Betty Pun, Atmospheric and Environmental Research, Inc
Development of a web-accessible relational database for air toxics and $PM_{2.5}$ based on the RIOPA study. (Completed)

RFSA 06-5: PILOT STUDIES FOR JUNIOR INVESTIGATORS ON THE HEALTH EFFECTS OF AIR POLLUTION
Marc Williams, University of Rochester
Determination of the effects of ambient particulate matter on toll-like receptor signaling and function in human dendritic cells. (Unpublished Report)

RFPA 06-4: HEALTH EFFECTS OF AIR POLLUTION
Murray Johnston, University of Delaware
Selective detection and characterization of nanoparticles from motor vehicles. (Report No. 173)
Simon Wong, University of Arizona
The molecular effects of diesel exhaust particulates on respiratory neutral endopeptidase. (Report No. 159)

RFA 06-3: WALTER A. ROSENBLITH NEW INVESTIGATOR AWARD
Charles Stanier, University of Iowa
Development and application of a personal exposure screening model for size-resolved urban aerosols. (Completed)
Yifang Zhu, Texas A&M University
Assessing children's exposure to ultrafine particles from vehicular emissions. (Completed)

RFA 06-2: ADDITIONAL HEALTH EFFECTS ENDPOINTS DURING THE CHRONIC BIOASSAY
Jeffrey Bemis, Litron Laboratories
Genotoxicity of inhaled diesel exhaust: examination of rodent blood for micronucleus formation. (Report No. 166, Part 2; Completed)
Daniel Conklin, University of Louisville
Effects of diesel emissions on vascular inflammation and thrombosis. (Report No. 166, Part 4; Completed)
Lance Hallberg, University of Texas Medical Branch
Assessment of the genotoxicity of diesel exhaust from improved diesel engines. (Report No. 166, Part 3; Completed)
Qinghua Sun, Ohio State University
Diesel exhaust exposure and cardiovascular dysfunction: ROS mechanism. (Study terminated)
John Veranth, University of Utah
Lung cell gene transcription responses to diesel exhaust. (Study terminated)

RFP 06-1: EXPOSURE FACILITY AND CONDUCT OF A CHRONIC INHALATION BIOASSAY
Joe Mauderly, Lovelace Respiratory Research Institute
Development of a diesel exhaust exposure facility and conduct of a chronic inhalation bioassay in rats and 90-day study in mice. (Phase 3A: Communication 17; Phase 3B: Report No. 166, Part 1; 2013)

2006 SPECIAL STUDIES ON AIR POLLUTION, POVERTY, AND PUBLIC HEALTH

HEI Collaborative Working Group on Air Pollution, Poverty, and Public Health in Ho Chi Minh City
The effects of short-term exposure on hospital admissions for acute lower respiratory infections in young children of Ho Chi Minh City. (Report No. 169)

HEI Collaborative Working Group on Air Pollution, Poverty, and Public Health in Ho Chi Minh City
The relationship between personal and ambient exposures in Ho Chi Minh City. (Completed)

RFPA 05-3: HEALTH EFFECTS OF AIR POLLUTION

Robert Brook, University of Michigan
Pilot Study: Effect of ambient fine particulate matter exposure on coronary vascular function and myocardial perfusion. (Unpublished Report)

Eric Jordt, Yale University
Pilot study: TRPA1 channels in airway sensory nerve ending as mediators of the irritant effects of acrolein. (Unpublished Report)

Debra Laskin, Rutgers University
Role of TNF-alpha in diesel exhaust-induced pulmonary injury in elderly mice. (Report No. 151)

Qinghua Sun, Ohio State University
Pilot Study: Diesel exhaust particle effects on angiogenesis. (Unpublished Report)

Junfeng Zhang, University of Medicine and Dentistry of New Jersey
Molecular and physiological responses to drastic changes in PM concentration and composition. (Report No. 174)

RFA 05-2: WALTER A. ROSENBLITH NEW INVESTIGATOR AWARD

Christopher Paciorek, Harvard School of Public Health
Integrating monitoring and satellite data to retrospectively estimate monthly $PM_{2.5}$ concentrations in the eastern United States. (Report No. 167)

Qunwei Zhang, University of Louisville
Activation of endothelial cells and gene expression in lungs following exposure to ultrafine particles. (Completed)

RFA 05-1B: CONDUCTING PLANNING OR DEMONSTRATION STUDIES TO DESIGN A MAJOR STUDY TO COMPARE CHARACTERISTICS OF PARTICULATE MATTER ASSOCIATED WITH HEALTH EFFECTS

JoAnn Lighty, University of Utah
A planning study to investigate the impacts of dust and vehicle-related PM on acute cardiorespiratory responses in the arid Southwest. (Unpublished Report)

RFA 05-1A: CONDUCTING FULL STUDIES TO COMPARE CHARACTERISTICS OF PM ASSOCIATED WITH HEALTH EFFECTS

Morton Lippmann, New York University
Characteristics of PM associated with health effects. (Report No. 177)

Sverre Vedal, University of Washington
Integrated epidemiologic and toxicologic cardiovascular studies to identify toxic components and sources of fine PM. (Report No. 178)

RFPA 04-6: HEALTH EFFECTS OF AIR POLLUTION

Marc Baum, Oak Crest Institute
Significance of highly toxic secondary emissions from on-road vehicles. (Completed)

Johannes Filser, GSF-Forschungszentrum für Umwelt und Gesundheit
Pilot study: Quantification of oxidative stress resulting from ambient air; contribution of specified compounds. (Unpublished Report)

Ian Kennedy, University of California, Davis
The uptake of ultrafine particles by vascular endothelial cells and inflammation. (Report No. 136)

Robert Lux, University of Utah
Air pollution effects on ventricular repolarization. (Report No. 141)

John Repine, University of Colorado
Pilot Study: Toxicity of inhaled carbonaceous particles generated under low air-fuel combustion ratio. (Unpublished Report)

Isabel Romieu, Instituto Nacional de Salud Pública
Multi-city study of air pollution and health effects in Latin America. (Report No. 171)
Holger Schulz, GSF-Forschungszentrum für Umwelt und Gesundheit
Pilot study: Systemic effects of inhaled ultrafine particles on the progress of inflammatory and cardiovascular disease. (Unpublished Report)
Simon Wong, University of Arizona
Pilot study: The molecular effects of diesel exhaust particulates on respiratory neutral endopeptidase. (Unpublished Report)

RFA 04-5: WALTER A. ROSENBLITH NEW INVESTIGATOR AWARD
Jonathan Levy, Harvard School of Public Health
Using geographic information systems to evaluate heterogeneity in indoor and outdoor concentrations of particle constituents. (Report No. 152)
Timothy Nurkiewicz, West Virginia University
Pulmonary particulate matter exposure and systemic microvascular function. (Report No. 164)

RFA 04-4: MEASURING THE HEALTH IMPACT OF ACTIONS TAKEN TO IMPROVE AIR QUALITY
Frank Kelly, King's College of London
The London low emission zone: assessing its impact on air quality and health. (Report No. 163)
Richard Morgenstern, Resources for the Future
Accountability assessment of the Clean Air Interstate Rule. (Report No. 168)
Curtis Noonan, University of Montana
Assessing the impact on air quality and children's health of actions taken to reduce $PM_{2.5}$ levels from woodstoves. (Report No. 162)
Jennifer Peel, Colorado State University
Impact of improved air quality during 1996 Atlanta Olympic Games on multiple cardiorespiratory outcomes. (Report No. 148)
Chit-Ming Wong, University of Hong Kong
Impact of the 1990 Hong Kong Legislation for restriction on sulfur content in fuel. (Report No. 170)

RFPA 04-3: HEALTH EFFECTS OF AIR POLLUTION
Michael Oldham, University of California at Irvine
Pilot study: Dosimetry in compromised animal models of human disease. (Unpublished Report)
Maria Morandi (Marek Radomski), University of Texas
Pilot study: Mechanisms of PM-associated exacerbation of endothelial dysfunction. (Study terminated)
James Robins, Harvard School of Public Health
New statistical approaches to semiparametric regression with application to air pollution research. (Completed)

RFA 04-2: WALTER A. ROSENBLITH NEW INVESTIGATOR AWARD
Michelle Bell, Yale University
Assessment of the mortality effects of particulate matter characteristics. (Report No. 161)
Michaela Kendall, Uludag University
Molecular absorption at PM surfaces; a compelling PM toxicity mediation mechanism. (Unpublished Report)

RFA 04-1: MEASURING THE HEALTH IMPACT OF ACTIONS TAKEN TO IMPROVE AIR QUALITY
Frank Kelly, King's College London
Congestion charging scheme in London: assessing its impact on air quality and health. (Report No. 155)

RFA 2004: TIME-SERIES OF AIR POLLUTION AND MORTALITY IN INDIAN CITIES
Kalpana Balakrishnan, Sri Ramachandra Medical College
Estimation of health effects of air pollutants using exposure-response functions from time-series analyses in Chennai, India. (Report No. 157, Part 1)
Rajesh Kumar, Postgraduate Institute of Medical Education & Research
A time-series study on the relation of air pollution and mortality in Ludhiana city, India. (Study terminated)
Uma Rajarathnam, The Energy and Resources Institute
Time-series study on air pollution and health in New Delhi, India. (Report No. 157, Part 2)

APPENDIX C: QUALITY ASSURANCE / QUALITY CONTROL PROCEDURES FOR HEI STUDIES

PART 1. GENERAL QUALITY ASSURANCE / QUALITY CONTROLPROCEDURES

1.1. POLICY STATEMENT

The mission of the Health Effects Institute (HEI) is to provide high-quality, impartial, relevant scientific information on the health effects of pollutants from motor vehicles and other sources in the environment. All funded HEI studies are expected to have adequate QA/QC procedures in place to ensure that the data are collected according to a written protocol and Standard Operating Procedures (SOPs) and are traceable. The QA/QC guidelines provided in this appendix apply to all HEI-funded studies. For studies that involve human subjects and some animal studies of regulatory significance, HEI will implement Special Quality Assurance Procedures (described in Part II) that include an external audit by an HEI selected audit team. HEI will inform the investigator after approval of the study whether the Special QA procedures will apply to his/her study.

1.2. QUALITY ASSURANCE / QUALITY CONTROL COMPONENTS

QA procedures begin with the planning phase of the raw data collection and follow the subsequent transformations of the data. Generally, HEI requires that the investigators:

- Use a written protocol
- Use written standard operating procedures
- Involve qualified personnel
- Maintain written records
- Use appropriate data processing techniques
- Use quality control procedures for all data collected

A. ***A written research protocol*** defines the experimental objectives, research strategy, and methodologies to be used. The protocol will be sufficiently complete and detailed as to ensure that the data collected are of known and documented quality. It will include, as applicable:

1. Name of Principal Investigator and co-investigators
2. Study objectives
3. Scientific background and rationale
4. Anticipated significance of study results
5. Description of all experiments to be conducted with reference to a particular standard operating procedure when appropriate (see *Section B*)
6. Methods of data processing (see *Section E*)
7. Internal quality control procedures to be used (see *Section F*)
8. Safety precautions needed
9. Plans for archiving the completed project, including the anticipated address and physical location for storage of all raw data, records, electronic media, reports, SOPs, and any specimens that are expected to be retained

For studies involving human subjects, the protocol should also contain:

10. Subject selection procedures to be used, including inclusion and exclusion criteria (when applicable)
12. Procedures used to maintain subject confidentiality
13. Copy of the blank form used to obtain Informed Consent from subjects
14. IRB approval

The protocol may be amended as necessary to accommodate changes to the experimental design. Any changes to the original protocol considering items 1 through 14 shall be made in writing by preparing an amendment to the protocol that is signed and dated by the Principal Investigator. See also *Section III, Roles of Institutions and Individuals in Achieving Quality Assurance*, below. All amendments must be approved by HEI.

B. *Written standard operating procedures* will be used to document all routine, critical experimental procedures and measurement techniques for which variability must be minimized. Critical experimental procedures are those procedures that result in the acquisition of experimental samples or data used to draw scientific conclusions. Generally, SOPs cover procedures that are done routinely over time by the same person or by different individuals to minimize procedural variation.

Standard operating procedures will be developed by individuals knowledgeable of the specific procedures. They will describe what, when, where, how, and why in a stepwise manner. They will be sufficiently complete and detailed to ensure that the data collected are of known and documented quality and integrity and are generated to meet measurement objectives such that there is a minimum loss of data due to out-of-control conditions. Routine quality control procedures should be covered by an SOP. Other items covered by an SOP might include: use and calibration of laboratory instruments, chemical sampling and analyses, preventive maintenance, data handling, maintenance and storage, etc.

Standard operating procedures will be uniquely identified and dated, and updated as needed. Copies of all current SOPs should be readily available for reference by the study team or by a third party, as needed. All SOPs that have been superseded will be maintained in a historical file. Deviations from SOPs should be documented.

C. *Qualified personnel* will conduct the proposed research. The qualifications of all participating individuals, and any training they receive for the conduct of the study along with prior experience, should be documented in resumes that will be maintained as a part of the permanent record of the project.

D. *Recordkeeping procedures.* Written records will be maintained to document all aspects of the research effort. This shall include the use of bound notebooks, standard forms, and computer input and output. All entries shall be made in indelible ink. The entries should be dated and signed or initialed by the individual making the entry. Notebook entries shall be made in chronological order. If a blank space is left between entries, it shall be crossed-hatched to render it unusable. Entries shall not be erased or otherwise obscured. If any entry is to be changed because it is in error or for any other reason, a single line will be drawn through the entry and a correction made in the margin. The altered entry shall carry an explanation of the reason for the change, the date of the change, and the initials or the signature of the individual making the change.

The Principal Investigator for the project shall periodically review the records to verify their completeness and accuracy. This review shall be documented by the Principal Investigator signing and dating the reviewed record.

E. *Data processing procedures* should be documented. Data processing includes all manipulations performed on raw (i.e. "as collected") information, validation, storage, transfer, reduction, and statistical analysis.

Data analysis frequently includes computation of summary statistics and their standard errors, confidence intervals, tests of hypotheses relative to the parameters, and model validation (goodness of fit tests). Specific statistical procedures, programs, and code to be used should be documented either in the protocol or in a separate document. HEI staff may require submissions of these procedures during the course of the study or the review of the final reports.

F. *Quality control procedures* should be documented for all data collected, i.e. procedures the investigator will use for ensuring the quality of the data during the data collection, sample analyses, and data processing.

1.3. ROLES OF INSTITUTIONS AND INDIVIDUALS IN ACHIEVING QUALITY ASSURANCE

The Principal Investigator and his/her institution have the primary responsibility for the preparation of the protocol, and all standard operating procedures and shall review and approve them by signing them. In addition, the Principal Investigator has the responsibility to prepare a Quality Assurance Plan, and submit it to HEI within the first months of the study (but no later than at the time of submission of the Year 1, 5-month progress report). HEI will work with the investigators to ensure that the QA plan is adequate and consistent with the agreed upon Statement of Work.

The QA plan shall include:

- The protocol, including the data analysis methods that will be used (see below)
- A list of SOPs
- A list of qualified personnel
- Record keeping procedures (how data will be collected, backed-up, collated, transferred, and stored)
- Documented data processing techniques
- Quality control procedures for all data collected

The protocol will be reviewed and approved by HEI. In many cases, the original Project Plan submitted with the HEI application can serve as the protocol, with added information as recommended by the HEI staff or the Research Committee. In some cases HEI may ask a group of investigators to work together to harmonize their study design and methods and develop a common or comparable protocol. Subsequent modifications to the protocol shall be submitted to HEI in the form of written amendments. All amendments are subject to HEI approval before they can be implemented.

The Principal Investigator has the responsibility for the actual conduct of the research, adhering to the protocol and SOPs. He or she has the primary responsibility of managing all aspects of data collection, validation, storage, transfer, reduction, and analysis. The Principal Investigator also has the responsibility for assuring that the research is conducted with qualified personnel and in accordance with this quality assurance plan. Technical and supporting personnel should have a detailed knowledge of the SOPs used in the conduct of their research activities.

HEI reserves the right to conduct a QA audit of an HEI-funded study if there are reasons to suspect that adequate procedures are not in place.

PART 2. SPECIAL QA/QC PROCEDURES

HEI uses third-party quality assurance (QA) procedures for most research projects involving human subjects and other projects with a high potential for use in regulatory decisions. The special procedures augment the QA/QC procedures applied to all HEI studies (described above in Part 1) and assure that data are collected under defined conditions and are reliable and traceable. Accurate scientific conclusions are dependent on the validity of the underlying data and the precision with which they are reported. If there is a QA program in place at the institute at which the research is being conducted, then HEI will assess its adequacy and modify its QA procedures as necessary.

2.1 THIRD-PARTY QA OVERSIGHT

HEI will generally engage one or more qualified individuals to serve as Quality Assurance consultants for the project. This individual will report to HEI's Director of Science and be responsible for overseeing the implementation of this Quality Assurance plan. The QA consultant will review the (draft) protocol for adherence to the QA requirements and notify HEI staff if modifications are necessary. The QA consultant shall maintain signed copies of the protocol and all SOPs.

The QA consultant may conduct periodic audits of the research while in progress and when it is completed to ascertain compliance with the HEI's special QA procedures. These audits shall include such matters as review of research procedures, notebooks, data forms, and data management activities. The audit shall be performed using the audit framework presented in the US Environmental Protection Agency's Guidance on Technical Audits and Related Assessment for Environmental Data Operations (EPA QA/G-7 2000, available at *www.epa.gov/quality/qs-docs/g7-final.pdf*).

2.2. ELEMENTS OF A QA AUDIT

The key elements of a QA audit include:

1. Opening Meeting with the audit team, the Principal Investigator, and key project personnel.

2. Observation of the project activities being performed by the personnel who regularly perform such activities.

3. Review of written documents, such as QA Plans, calibration readouts, process data readouts, sample logs, custody papers, instrument logs, printouts from data spreadsheets, and maintenance notebooks (such records may be in electronic form).

4. Interviews with the project personnel to verify the results of observation and to clarify issues noted during document review.

5. Objective Evidence Compilation, such as copies of notebook pages, logs, instrument and model outputs, and QC charts.

6. Closing Meeting, during which the QA consultant provides a verbal summary to the Principal Investigator of significant findings that need to be addressed.

7. QA Audit Report. The QA consultant prepares a "Business Confidential" report of the audit. The report shall detail the nature of the audit, significant findings, and any requirements for corrective action(s). The audit report shall be provided to the HEI Director of Science, who will then transmit it to the HEI project manager for transmission to and discussion with the Principal Investigator. If corrective action is required, the Principal Investigator will ensure that such action is taken and return the summary to the HEI project manager with a copy to the QA consultant noting the action(s) taken. All copies of the audit report are to be marked as "Business Confidential" and are to be destroyed after use or maintained in a

file separate from other records of the project. These audit reports are only to be released to people directly involved in management of the projects. To give these reports to people who are not directly involved violates the confidential nature of the audits and potentially reduce the degree of candor required in communications within the project on matters requiring corrective action. The QA consultant shall maintain a log of all audits indicating for each audit: the date conducted, participating personnel, and the nature of the audit.

2.3. TIMING OF QA AUDIT

While the exact timing of the audits varies across studies, the followed guidelines should be followed when defining the general plan and scope of the QA oversight for a study:

A. Audits during the course of the research period

1. Clinical studies

   One QA audit should be conducted at the beginning of Year 1 to ensure that all SOPs are in place, the protocol is followed, and a data management plan is in place. This audit should occur fairly early in the study so that problems, if found, can be remedied before too many subjects have been studied.

   One QA audit during Year 2 to audit a subset of the data collected to verify that the data management procedures are adequately implemented and the data collected are traceable, the informed consents are signed, and the protocol is followed consistently. This audit is optional and would depend on the outcome of the initial audit.

2. Epidemiologic, statistical, and other studies

   One audit at the end of Year 1 or during Year 2 to ensure that data collection is done according to the protocol, the data collected are traceable, and a data management plan is in place. If problems are encountered and not addressed adequately, a follow-up visit may be needed.

B. Audit of the final report

Unless there are specific reasons to expedite the review of a final report, the timing of the final report QA audit will be decided during the first discussion of the draft final report by the Review Committee. The following guidelines will be followed:

1. If the Review Committee thinks that the draft final report does not require additional analyses, then a QA audit of the draft report should be scheduled immediately so the investigators can address all issues raised by the auditors in the revised report.
2. If the Review Committee thinks that the draft final report requires substantive changes and/or (partial) reanalysis of the data, the QA audit should be conducted on the revised final report, as soon as it is received.
3. Regardless of the timing of the final report audit, the auditors should always be provided with the final "accepted" version of the report and asked to review it before issuing the final QA Statement, which will be printed in the final, published report.

APPENDIX D: HEI POLICY ON THE PROVISION OF ACCESS TO DATA UNDERLYING HEI-FUNDED STUDIES

The provision of access to data underlying studies of the health effects of air pollution is an important element of ensuring credibility, especially when the studies are used in controversial public policy debates. The open and free exchange of data is also an essential part of the scientific process. Therefore, *it is the policy of the Health Effects Institute to provide access expeditiously to data for studies that it has funded and to provide that data in a manner that facilitates review and validation of the work but also protects the confidentiality of any volunteers who may have participated in the study and respects the intellectual interests of the investigator in the work.*

This policy applies to all research funded by HEI, whether that research was funded prior to or after November 8, 1999, when amendments to OMB Circular A-110 took effect to require access under the federal Freedom of Information Act (FOIA) to data from federally-supported research that was used in developing a federal agency action that has the force and effect of law.

In responding to FOIA requests through the U.S. EPA or other federal agency for HEI data that are subject to the Circular A-110 amendments, HEI will follow the principles established in the amendments.

In responding to non-FOIA, direct requests to HEI for data, HEI will in general follow the principles described below, which are designed to be consistent with the principles contained in the recent A-110 Amendments, although specific cases may require other arrangements for providing access.

1. *Data* The data to be provided will vary from study to study, but in general will consist of the recorded factual material commonly accepted in the scientific community as necessary to validate research findings. It will not include any of the following: preliminary analyses, drafts of scientific papers, plans for future research, peer reviews, or communications with colleagues. The "recorded" material excludes physical objects (e.g. laboratory samples). Research data also excludes (a) trade secrets, commercial information, materials necessary to be held confidential by a researcher until published, or similar information which is protected under law; and (b) personnel and medical information and similar information the disclosure of which would constitute a clearly unwarranted invasion of personal privacy, such as information that could be used to identify a particular person in a research study. In some cases, where all of the data used is from publicly available data sets and the analytic data set can readily and expeditiously be recreated, HEI and/or the Investigator might provide detailed descriptions of how to access and use these public data sets to recreate the analytic data set in lieu of providing the full analytic data set.

2. *Timing* HEI will seek to provide access to data as expeditiously as possible after the completion and publication of the HEI Research Report (or Reports) resulting from the study. In doing so, HEI will, to the maximum practical extent, take into consideration the legitimate intellectual interests of the investigator to have the opportunity to benefit from his or her intellectual endeavors and to publish subsequent analyses from the data set (including additional analyses funded by HEI). In some cases, e.g. for studies of particularly high regulatory importance being used to inform decisions over a short time frame, HEI may need to work to balance the investigator's interests against the need for interested parties to obtain access in a timely manner.

3. *Responsibility and Reimbursement for Costs* To the maximum extent possible, HEI will encourage the Principal Investigator to be the primary sharer of the data. To the extent that providing the data would place an undue burden on the Investigator (e.g. in a situation where the sheer number of requests would not allow the Investigator to continue to conduct her or his research), HEI will be prepared to establish an alternative procedure for it to share the data. In either case, HEI will expect to receive from data requesters reasonable reimbursement for both the direct costs of providing the data, and for the time of the Investigator and/or HEI staff to gather, transmit, and explicate the data. In order to facilitate data access for all future and current studies in which HEI and the investigator expect that the results have a high likelihood of being used in supporting a regulatory decision, HEI will consider requests from the investigator for a reasonable budget of data archiving funds, to be provided as part of the project budget.

4. *Confidentiality* Any requester of data will be expected to obtain and adhere to all confidentiality approvals necessary to handle the data from the appropriate agencies (e.g. the National Center for Health Statistics). HEI will not knowingly itself provide, or require an investigator to provide, information that can be used to identify a specific individual.

5. *Responsibility of the Data Requester* In addition to the payment of reasonable costs and the obtaining of any necessary confidentiality approvals, HEI will ask the data requester, as would be normal courtesy in the scientific community, to inform both the Principal Investigator and HEI of any findings emerging from their analysis, to provide the Principal Investigator an opportunity to respond to those findings prior to publication, to provide copies to both the Principal Investigator and HEI of any papers submitted for publication from the data, and to cite both HEI and the Principal

Investigator in any publication, noting explicitly that the views expressed are those of the new analyst and not those of the Principal Investigator, HEI, or HEI's sponsors.

6. *HEI Decision Making* All requests for data will be reviewed and decided upon by a Committee of the HEI Science Director, and the Chairs of the HEI Research and Review Committees, in consultation with both the research and review staff scientists responsible for the study in question. Any significant policy questions arising from a particular request will be considered, upon recommendation of the Committee and the President, by the Board of Directors.

The provision of data will not be simple to accomplish and will at times raise concerns and controversy from one or more parties. HEI will attempt to provide data in a manner that to the maximum extent practical fosters an atmosphere of collegiality and mutual respect among all parties, with the aim of obtaining from the sharing of data the maximum benefit for science and for the quality of the public policy decision-making process.

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