Request for Applications

HEALTH EFFECTS INSTITUTE

January 2011

Winter 2011 Research Agenda

RFA 11-1 Health Outcomes Research – Assessing the Health Outcomes of Air Quality Actions

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 half of its core funds from the U.S. Environmental Protection Agency and half 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 280 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 200 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.

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INTRODUCTION

This booklet contains the Winter 2011 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.

REQUEST FOR APPLICATIONS 11-1: HEALTH OUTCOMES RESEARCH – ASSESSING THE HEALTH OUTCOMES OF AIR QUALITY ACTIONS

Request for Applications 11-1, described on pages 7–17, solicits applications for studies designed to assess the health impacts of actions taken to improve air quality, and to develop methods required for, and specifically suited to conducting, such research. Preference will be given to (1) studies that evaluate regulatory and other actions at the national or regional level implemented over multiple years; (2) studies that evaluate complex sets of actions targeted at improving air quality in large urban areas and major ports with well documented air quality problems and programs to address them; and (3) studies that develop methods to support such health outcomes research.

The submission and review of applications for RFA 11-1 will entail a two-stage process.

- Investigators are strongly encouraged to submit a **Preliminary Application by May 18, 2011**. The HEI Research Committee will discuss the preliminary applications and will provide feedback by the end of June. Investigators who do not submit a preliminary application should submit a **Letter of Intent by July 13, 2011.**
- All investigators should submit a **Full Application by August 17, 2011**. Full applications will be reviewed by a Special Review Panel before consideration by the Research Committee.

Investigators who are applying for a research project that is time-sensitive should notify HEI as soon as possible.

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 the debate between 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 half of its core funds from the EPA and half 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. Applications to major RFAs are reviewed first for scientific quality by an ad hoc panel of appropriate experts. They are then reviewed by the HEI Research Committee both for quality and relevance to the goals of the research program.

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, and invited guests 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 25–28.

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 Statement or 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 27–28.

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. 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**. HEI recently initiated new research to test the effects of ozone and PM 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**. HEI held a workshop in December 2009 to identify challenges and opportunities for further research on accountability. Key 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 are 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 new Strategic Plan on research priorities and plans for implementing them. The entire plan is available on HEI's website, *www.healtheffects.org/funding.htm*.

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.

RFA 11-1: HEALTH OUTCOMES RESEARCH – ASSESSING THE HEALTH OUTCOMES OF AIR QUALITY ACTIONS

INTRODUCTION

The Health Effects Institute (HEI) is seeking to fund research to assess the health outcomes of air quality actions. Request for Applications (RFA) 11-1 solicits applications for studies designed to assess the health effects of actions to improve air quality and to develop methods required for, and specifically suited to, conducting such research. Preference will be given to

(1) studies that evaluate regulatory and other actions at the national or regional level implemented over multiple years;

(2) studies that evaluate complex sets of actions targeted at improving air quality in large urban areas, including those in the vicinity of major ports, with well documented air quality problems and programs to address them; and

(3) studies that develop methods to support such health outcomes research.

Proposed studies are expected to contribute to the scientific knowledge in addition to evaluating whether a particular action has been effective in decreasing exposure and improving public health. This RFA will consider study designs that are either prospective or retrospective; however, HEI specifically encourages investigators to submit proposals for prospective studies to address an important gap in directly linking health outcomes research to upcoming regulatory actions. Investigators are expected to work in multidisciplinary teams and, where appropriate, devote part of their efforts towards methods development.

Within the focused areas of research outlined above, HEI supports the inclusion of international research if it can be shown that the results are likely to inform the regulatory decision-making process in the United States. In addition, as indicated in the HEI Strategic Plan 2010–2015 (Health Effects Institute 2010a), HEI encourages the evaluation of susceptible populations and exposure and health disparities issues, and would consider evaluation of air quality actions that are also designed to address climate change. RFA 11-1 does not solicit studies to evaluate short-term, small-scale regulatory actions. However, investigators who have identified a unique opportunity to evaluate a specific short-term intervention are encouraged to apply through Request for Preliminary Applications (RFPA) 10-3.

RFA 11-1 is a continuation of efforts by HEI and other organizations to support health outcomes research (previously termed accountability research). The initial HEI Communication 11, Assessing Health Impact of Air Quality Regulations: Concepts and Methods for Accountability Research (HEI Accountability Working Group 2003) set out a conceptual framework for assessing the health effects of air quality regulations, identified the types of evidence required by the framework, and described the methods by which that evidence can be obtained. Based on that framework, HEI funded an initial program of nine studies. Communication 14, HEI's Research Program on the Impact of Actions to Improve Air Quality: Interim Evaluation and Future Directions (van Erp and Cohen 2009) provides a summary of the approaches taken in those studies as well as an overview of preliminary results. HEI has published the reports from some of these studies; reports based on other studies will become available during 2011.

Valuable lessons learned in conducting the initial set of studies funded by HEI and other organizations can inform the next wave of health outcomes research. Communication 15, Proceedings of an HEI Workshop on Further Research to Assess the Health Impacts of Actions Taken to Improve Air Quality (Health Effects Institute 2010b) provides a summary of lessons learned to date and identifies knowledge gaps that remain to be addressed, leading to a set of recommendations for future research. In exchanges with the research community and with government and industry stakeholders, HEI has distilled the workshop recommendations into the focused goals of the current RFA. HEI expects to fund up to six proposals and devote approximately $2.5 million to this research over 3 years.

BACKGROUND

Interest in assessing the health effects of air quality actions has grown in response to questions about the benefit of tightening air pollution regulations. Since the 1980s, measurements at thousands of monitoring stations across the country have shown reduced concentrations of all six criteria pollutants. This progress is, of

course, associated with a price. The U.S. Environmental Protection Agency (EPA) estimated that from 1970 to 1990 the cost of air pollution control was about $25 billion per year — more than $500 billion over 20 years. Even as new research has strengthened evidence for both adverse health effects due to air pollution and the case for regulatory and other preventive measures, and even as estimates of health benefits have found that the estimated benefits exceed the estimated costs (Office of Management and Budget 2010), policy makers, legislators, industry representatives, and the EPA continually seek to document whether past efforts to reduce air pollution have yielded demonstrable improvements in public health and to better predict whether future efforts will continue to do so. More recently, interest in assessing the health effects of air quality actions is reflecting a growing appreciation among stakeholders and the scientific community of the need to evaluate the health outcomes of actions taken to slow climate change (e.g., Smith et al. 2009). These outcomes may result from the primary health effects of reducing air pollution and the potential effects on health of reductions in the pace and ultimate extent of climate change, so-called co-benefits.

Health outcomes research requires assessing the effectiveness of regulations and other actions to reduce emissions and determining whether emission reductions have affected ambient concentrations and personal exposure to pollutants as intended. It must then extend to the prevention of adverse health effects from personal exposure. National governments and public health agencies have attempted to quantify past health benefits of air quality improvement and to estimate future effects. These assessments have generally relied on risk estimates from epidemiologic studies to calculate public health outcomes under air quality scenarios that reflect either the continuation of past exposure patterns or future exposure patterns assuming more stringent air pollution control (Environmental Protection Agency 1999). However, such estimates need to be validated against the outcomes in real world studies of actual regulatory programs and other interventions. Due to the considerable challenges inherent in such research, few studies have been undertaken to date (e.g. Chay and Greenstone 2003; Auffhammer et al. 2009; Pope et al. 2009; Harrington et al. 2010; Moore et al. 2010). Further development of suitable epidemiologic and statistical approaches is needed to support the evaluation of long-term regulatory actions.

Efforts to measure the consequences of air quality regulations and other actions remain challenging. Air quality actions are often taken asynchronously at multiple levels (e.g., national, state, and local). Diverse approaches are therefore needed to evaluate the outcomes of these actions on a variety of temporal and geographic scales. The consequences of interventions may also extend beyond changes in air quality. Whether or not an intervention improves air quality, it may result in changes in personal activities and behaviors or in economic activities (or other factors) that may affect health. Therefore, it may be difficult to isolate the causal pathways leading from regulation and its consequences for air quality to a change in health risk. The adverse health effects that may be caused by exposure to air pollution can also be affected by other factors (such as health care and medical practices, some of which can change over the same time frames as air pollution concentrations) and by other exposures (such as those from indoor sources).

Regulatory interventions to improve air quality, especially large national programs such as the U.S. Clean Air Act, may not have immediate effects on either air quality or public health. Ensuing changes in emissions, ambient concentrations, and human exposure may not be demarcated sharply in space or time, and the dynamics of biological processes of injury that underlie adverse health effects of air pollution may not directly follow the changes in exposure that result from regulatory action. The longer the time between promulgation of a regulation and its effects, the greater the possibility that other factors that influence health outcomes may come into play and interfere with demonstrating the effects of the intervention itself. The degree to which the regulation is enforced may further complicate the analysis by extending the anticipated time between intervention and effect.

HEI Communications 14 (van Erp and Cohen 2009) and 15 (Health Effects Institute 2010b) provide an overview of the challenges posed in evaluating long-term regulatory actions (such as National Ambient Air Quality Standards [NAAQS] and emissions regulations) as well as the importance of appropriately adjusting for confounders that may well act on the same time-scale as the intervention, e.g. changes in population demographics. Efforts to systematically collect air quality and health outcomes data are of crucial importance to evaluate national- and regional scale programs (e.g. Medina et al 2009; Matte et al. 2009). In addition, developing methods and tracking systems for changes that affect public health (e.g., medical practice, standard of living, lifestyle, and diet) is important for adequate assessment of the efficacy of standards and regulations that have effects over longer time periods.

Studies of the health effects of air quality improvement programs implemented over short time frames (e.g., Clancy et al. 2002; Hedley et al. 2002) suggest that the outcomes of such interventions may be directly measurable after a relatively short time period if a substantial change in air quality is produced. However,

other studies, most notably of interventions aimed at reducing traffic congestion, have found only small improvements in air quality that preclude a direct evaluation of health effects due to lack of statistical power (Kelly et al. 2011, in press), or have found that the observed air quality changes were regional in nature and could not be directly related to the intervention at the local level (Peel et al. 2010). At this time, HEI is not soliciting applications of shorter-term or small-scale actions because the value of conducting additional retrospective studies of such actions may be limited, especially if the time period is relatively short and the air quality actions are only temporary (Health Effects Institute 2010b). However, some studies may remain useful under specified circumstances, e.g. prospective longitudinal panel studies that evaluate biomarkers of exposure or effect that may coincide with a substantial improvement in air quality (e.g. Zhang et al. 2010). Investigators who have identified a unique opportunity to evaluate a specific short-term intervention are encouraged to apply through RFPA 10-3 (available at *www.healtheffects.org/funding.htm*).

OBJECTIVES OF RFA 11-1

OVERALL OBJECTIVES

1. Fund studies to assess the health effects of regulatory and incentive-based actions taken to improve air quality, with a focus on
   a) National- or regional-scale regulatory actions over multiple years; and
   b) Complex sets of regulations targeted at large urban areas, including those in the vicinity of major ports, with well documented air quality problems and programs to address them;
2. Develop methods required for, and specifically suited to, conducting such research.

SPECIFIC OBJECTIVES

Studies to Assess the Health Effects of Long-term Regulatory Actions to Improve Air Quality

RFA 11-1 seeks proposals to study the effects of specific regulatory programs to improve air quality, with a focus on (1) large-scale, multiyear programs and (2) complex programs aimed at large urban areas and major ports. Such air quality intervention programs are intended to produce changes in emissions, ambient pollutant concentrations, exposures, and, ultimately, health outcomes (HEI Accountability Working Group 2003). Proposed studies should be designed to measure changes in human exposure and in health status or risk of health effects in populations that are the intended beneficiaries of these actions, including those which may be at particular risk from air pollution due to greater than average exposure or susceptibility. Investigators are also encouraged to address disparities in exposure and health outcomes related to ethnicity and socio-economic status, where appropriate. Proposed studies should document in detail the measured or projected effects of specific interventions or groups of interventions on emissions and ambient concentrations in order to demonstrate that a considerable enough change has occurred (or is expected to occur) to have the potential to produce a measurable change in human exposure and effects and to allow for assessment of changes in health outcomes (see *Critical Study Design Considerations* below).

RFA 11-1 is intended primarily to estimate the outcomes of actions taken in the United States. Proposals for studies of actions taken in countries other than the United States will be considered, but such studies should be relevant to current U.S. conditions (e.g., studies of interventions at comparable ambient levels to reduce emissions from sources commonly found in the U.S.). Both studies with prospective as well as retrospective designs will be considered; however, HEI specifically encourages investigators to submit proposals for prospective studies to address an important gap in directly linking health outcomes research to upcoming regulatory actions. Considering general trends in regulations and air pollution research, HEI encourages approaches that consider more than one pollutant; for example, study designs that take into consideration changes in one pollutant that is the target of a specific regulatory action as well as changes in co-pollutants that may have been affected as well. Approaches to assess programs to improve air quality that are also designed to address climate change will be considered.

The following sections outline specific areas of interest targeted under this RFA, as specified in the overall objectives, as well as general study design considerations.

National- or Regional-Scale Regulatory Actions Over the Long Term

The EPA is currently implementing a number of major regulatory actions, including the on-road and off-road diesel rules, rules covering locomotives and marine vessels, and the existing Clean Air Interstate Rule (CAIR), which targets air pollution that cross state boundaries (see *Targets of Opportunity*). In addition, the EPA is

considering a number of new regulations, including Maximum Achievable Control Technology (MACT) standards for utilities and industrial boilers, and the Clean Air Transport Rule, a replacement of CAIR. Individual states and regions are also implementing or planning regulations covering a number of important sources of air pollution, including actions to reduce emissions in major ports and transportation corridors (as discussed in more detail below).

Ideally, health outcomes research would be incorporated into policy development. This process may include an iterative cycle of prospective and retrospective analysis, whereby potential outcomes of policies are evaluated using exposure and risk assessment models during the initial policy development phase, and the results of policies are evaluated once air pollution reduction strategies have been implemented. Investigators are encouraged to consult with government agencies to look for opportunities to incorporate health outcomes research at an early stage. Any study planned in this fashion will need to assess the availability of high quality data on baseline conditions of air quality, exposure, and health for comparison against post-intervention measurements.

TARGETS OF OPPORTUNITY

Continually changing air pollution regulations in the United States, Europe, and elsewhere offer opportunities for health outcomes research on national, regional, state, and local scales. As HEI learns of new targets of opportunity for health outcomes research, they will be listed on a dedicated Web page so that the research community can respond to them in a timely fashion.

In the United States, potential targets of opportunities to evaluate the outcomes of **long-term regulatory actions** include:

* ***Implementation of National Ambient Air Quality Standards (NAAQS) for $PM_{2.5}$ and Ozone*** State implementation plans (SIPs) being developed in the United States could serve as the basis for *prospective* health outcomes studies. Such studies could utilize existing ozone measurements and the extensive data on nationwide concentrations of particulate matter less than 2.5 μm in aerodynamic diameter ($PM_{2.5}$) that are being collected from the Interagency Monitoring of Protected Visual Environments (IMPROVE) program and the $PM_{2.5}$ Chemical Speciation Monitor Network to establish baseline conditions against which future emissions reductions could be assessed. The SIP process could also serve as the basis for comprehensive assessments that address changes in emissions, ambient pollutant concentrations, population exposures or doses, and, ultimately, health outcomes.

* ***Clean Air Interstate Rule*** The CAIR was issued in 2005 to dramatically reduce air pollution that moves across state boundaries. CAIR permanently caps emissions of sulfur dioxide (SO_2) and nitrogen oxides (NO_x) across 28 eastern states and the District of Columbia. When fully implemented, CAIR was designed to reduce SO_2 emissions in these states by over 70 percent and NO_x emissions by over 60 percent from 2003 levels, resulting in substantial reductions in premature mortality and improved visibility by 2015. After substantial litigation which invalidated parts of the CAIR, EPA has issued a proposed Clean Air Transport Rule to replace CAIR. A closely related action was the Clean Air Mercury Rule (CAMR), which has also been set aside by the courts; EPA is currently preparing a MACT Rule for mercury and possibly other emissions from from coal-fired electric utilities. Together, CAIR (and its replacement, the Transport Rule) and the upcoming Air Toxics rule create a multi-pollutant strategy to reduce emissions from stationary sources.

* ***Regulations Affecting Engine Technologies and Fuels*** In view of challenges presented by climate change and air quality, new fuel and technologies are being introduced at an unprecedented rate (HEI 2011). Examples of technologies include gasoline direct injection and power train electrification, and of fuels include ethanol, other alcohols, and natural gas. The changes in emissions and air quality brought about by the introduction of such technologies and fuels may also provide useful opportunities to examine their impact on emissions, exposure and health effects. The reductions in emissions due to the regulations, some of which are listed below, provide an opportunity to assess changes in exposure and

health outcomes in populated areas that are heavily affected by traffic. It may be useful to consider repeating some previous tunnel studies (e.g. Gertler et al. 2002) to document fleet turnover and changes in emissions due to changing technologies. Changes in emissions from traffic can then be used to estimate changes in exposure for populations living close to major traffic corridors.

- ***Heavy-Duty Diesel/Low Sulfur Fuel Rule*** In 2001, the EPA promulgated regulations to reduce heavy-duty diesel-vehicle emissions by reducing fuel sulfur content and implementing emission reduction controls (e.g., particle traps and various technologies for reducing NO_x). The Highway Diesel Rule included a step change in sulfur content limits for diesel fuel from 500 ppm to 15 ppm effective July 1, 2006, and a more gradual introduction of new heavy-duty vehicles with added emissions controls in model years 2007 and 2010.
- ***Tier II Regulations for Light and Medium Duty Vehicles and Fuels*** From 2004 through 2009, the EPA implemented a substantial tightening of the emission standards for light- and medium-duty on-road vehicles. These standards require, among other features, substantial reductions in emissions of volatile organic compounds (VOCs) and nitrogen monoxide (NO), reduction of sulfur in gasoline to an average of no more than 30 ppm, and application of the same standards to medium-duty as well as light-duty vehicles. Some of these changes are taking place over a long time (i.e., at the rate of introduction of new vehicles) whereas others, especially the substantial lowering of sulfur in gasoline, has taken place over a much shorter interval for all gasoline sold in the United States.
- ***California Diesel Emissions Reductions Programs*** California is implementing a number of programs to reduce emissions from existing and new diesel engines used for on-road, nonroad, and stationary purposes. These include funding programs (e.g., the Moyers program to fund retrofits and replacements of school buses and other diesel vehicles) as well as a range of regulatory initiatives (California Air Resources Board 2000). These efforts are intended to result in both near-term and longer-term reductions in emissions and exposures.
- ***Diesel Emissions Reduction Act (DERA)*** EPA has been implementing this act over the past several years, providing substantial funding (~$50 million/year rising to $300 million in the recent Recovery Act) to fund the replacement and retrofit of older diesel trucks and buses.
- ***Efforts to Improve Fuel Quality and Fuel Characteristics*** Over the past decades, a number of efforts have been taken to improve the characteristics of gasoline. These include, among others, introduction in January 1995 of Reformulated Federal Gasoline in major metropolitan areas (which among other changes required a substantial reduction in benzene content and increase in oxygen content) and, in a number of states, introduction of gasoline with reduced volatility. In addition to these potential retrospective opportunities, recent efforts to reduce use of MTBE as an additive and to substantially increase use of ethanol may pose additional opportunities to measure changes in human exposure and health effects.

* ***Air Toxics Control Actions*** The EPA is required to assess the health risks and (if necessary) control the ambient levels of 188 hazardous air pollutants, or *air toxics*, and has issued MACT controls for a number of industries and controls of smaller "area sources" (e.g. of dry cleaning facilities). Most recently, EPA has proposed a major industrial boiler and incinerator MACT rules. Health outcomes research concerning these air toxics might include longitudinal measurements of emissions and ambient concentrations and identification of health endpoints that could be tracked in the near term. This approach is probably most suitable for hazardous air pollutants associated with short-term effects (e.g., irritant responses for which there are well established biomarkers of personal exposure or effects).

Regulatory Actions Targeted at Large Urban Areas and Major Ports

Included among the studies solicited under RFA 11-1 are those to evaluate the effectiveness of complex programs targeted at reducing emissions in large urban areas, including those in the vicinity of major ports, in improving public health of populations affected by those emissions, achieved through a combination of federal

regulations and state or regional air quality programs. Studying such complex actions requires understanding of the sets of rules being implemented and their timeline of implementation, estimation of the emissions reductions over multiple years, as well as actual, good quality monitoring data over the study period.

Relatively rapid changes in ambient pollutant concentrations may occur in a localized area as a result of a major change in local source emissions due to regulatory action. Numerous opportunities exist for studies of such interventions throughout the United States and elsewhere. For example, since 2001 the New York City Metropolitan Transit Authority (MTA) has operated its diesel bus fleet using fuel with ultralow sulfur levels and has been phasing in diesel filter trap technology for those buses. In addition, the MTA has converted portions of its bus fleet from diesel to natural gas. Each of these actions potentially reduces neighborhood concentrations of diesel-related particle components and thereby potentially affects health outcomes. Because local interventions occur within relatively compressed temporal and spatial domains, studies that aim to document cause-effect relations between local reductions in emissions and changes in exposure and health outcomes may be economically and logistically feasible.

Recently, California, New York, and other states have implemented or begun to implement programs aimed at reducing emissions from the "goods movement" sector. Examples are complex regulations targeted at major ports, such as the ports of Houston, Los Angeles/Long Beach, New York/New Jersey, Oakland, and the combined air shed of Seattle/Tacoma & Vancouver (see *Useful Web Sites* below). Major ports are serviced by marine vessels, harbor craft, railway locomotives, heavy-duty trucks, and cargo handling equipment and are large contributors to concentrations of particulate matter and nitrogen oxides, mostly from diesel engines. In addition, ports are often situated in, or close to, densely populated areas, with a relatively high percentage of disadvantaged populations (National Environmental Justice Advisory Council 2009). Air quality management programs in ports have to target multiple sources in order to be effective: measures may include providing shore power for ocean-going vessels while docked in the harbor, reducing sulfur concentrations in marine fuel, reducing maximum speed when ships approach or leave the harbor, and targeting emissions from heavy-duty trucks, locomotives, and non-road equipment through requirements for aftertreatment on new diesel engines and retro-fitting of older engines (see e.g. California Air Resources Board 2006).

In addition to such targeted state and local plans, certain federal regulations also affect emissions in the port areas. For example, the EPA is targeting on-road and non-road emissions through the following (proposed) regulations:

- Highway heavy-duty diesel engines: the 2007 Highway Diesel Rule (see text box: Targets of Opportunity);
- Shipping. Clean Air Act (CAA) engine and fuel standards for ships became effective in April 2010, with near-term standards for newly-built engines starting in 2011 and long-term standards requiring an 80 percent reduction in NOx emissions starting in 2016. In addition, the EPA and Environment Canada proposed an Emissions Control Area (ECA) for specific portions of U.S. and Canadian coastal waters to reduce NOx, SOx, and PM emissions from the marine sector. In March 2010, the International Maritime Organization officially designated waters off North American coasts as an area in which stringent international emission standards will apply to ships. In support of the ECA, the quality of fuel that complies with the ECA standard will change over time: starting in 2012, shipping fuel cannot exceed 10,000 ppm sulfur and starting in 2015 it cannot exceed 1,000 ppm.
- Railway locomotives. Locomotive engines being produced today must meet relatively modest emission requirements set in 1997, but continue to emit large amounts of NOx and PM. In May 2004, as part of the Clean Air Nonroad Diesel Rule, the EPA finalized new requirements for nonroad diesel fuel that will decrease the allowable levels of sulfur in fuel used in locomotives by 99%. In March 2008, the EPA finalized a three part program that will substantially reduce PM (90% reduction) and NOx (80% reduction) emissions from diesel locomotives. The rule applies to emissions from remanufactured existing locomotives starting in 2008 and newly-built locomotives, includes idle reduction requirements, and establishes long-term standards for newly-built engines beginning in 2015.
- Other nonroad vehicles. Construction equipment and other nonroad vehicles are affected by the above mentioned Clean Air Nonroad Diesel Rule, requiring introduction of less polluting engines and fuel across several transportation sectors.

HEI welcomes research proposals to evaluate coordinated, complex emissions reductions programs in urban areas with concentrated exposures, e.g. programs targeted at specific transportation corridors or hubs, as well as proposals to specifically evaluate health outcomes of reducing emissions in ports.

Critical Study Design Considerations

HEI Communication 14 (van Erp and Cohen 2009) and 15 (HEI 2010b) identify in detail a range of important design considerations for all health outcomes research. A number of these considerations are summarized below. The ability of any proposed study in response to this RFA to address and integrate these considerations will be a central factor in decisions on funding.

Pre-intervention baseline. Studies of planned actions to improve future air quality (a prospective study design) and studies of actions taken in the past (a retrospective study design) will both be considered. In either case, investigators will need to be able to document baseline (i.e., pre-intervention) air quality and health conditions. Prospective studies are potentially the most informative but will usually require that investigators identify proposed actions in advance and begin work early enough to provide stable estimates of baseline conditions. Because the duration of HEI-funded studies is limited to three years, prospective studies of long-term air quality actions should be designed in stages that can be funded separately. If this is the case, the proposal should identify a clear set of deliverables for each stage.

Confounding by other long-term changes. Studies of U.S.- or state-wide programs enacted over recent decades may benefit from using existing cohorts or other populations for which suitable historical data exist. In such studies, the need to account for secular trends in health risk factors other than air pollution will be both critical and challenging. For example, regulatory interventions to improve air quality may result in changes of behavior within target populations that may in turn affect exposure and dose. In addition, other factors changing in the same time period as the air quality improvement could affect public health and confound the estimation of effects of the regulation or other intervention.

The lengthy time period of interest requires consideration of 1) the time lag between the propagation of a regulatory change and the time at which any effect of the regulation can be expected to occur; 2) long-term temporal trends in population structure (e.g., demography) that alter the susceptibility of the population to various adverse health outcomes; 3) changes in medical access as well as public health practices that lead to improved outcomes for particular diseases; 4) changes in the distribution of health-related behaviors within and among populations; 5) effects of regulatory changes for a given pollutant on the overall mixtures to which populations are exposed; and 6) the often heterogeneous patterns of change in pollutant levels due to a regulatory action across time and space.

Researchers designing studies of the health effects of regulations should anticipate the possibility of such changes and develop approaches to deal with them (such as surveys to first characterize baseline behavior or exposure and to then track changes in time-activity patterns and other factors that could affect exposure or health outcomes). Applicants should indicate the types of factors they consider important and discuss how they would address them in their studies. The cooperation of public agencies and officials may be required to ensure study success; investigators should provide documentation of such cooperation. These agencies might include state and local air monitoring and regulatory agencies and/or public health agencies involved in the development of health tracking programs (see Matte et al. 2009). For some applications, cooperation of affected industries and community organizations may also be needed.

Exposure estimation. During the design phase, future health outcome studies should consider carefully the predicted pollutant concentration and exposure reductions anticipated from an intervention. Proposals should present detailed estimates of the predicted air quality changes and the power of the study to detect associated changes in health outcomes. If only a limited reduction is expected, emphasis might be given to the "upstream" components of the accountability chain: emission reductions, air quality improvements, and perhaps also personal exposure, before a decision is made whether direct measurement of health outcomes will provide meaningful results.

In addition, careful assessment of available monitoring sites and data quality is needed. The number and location of monitors, which pollutants are measured, and the frequency of sampling may determine the power of the study to detect changes in air quality. This is especially true of traffic interventions which may cause relatively small changes in urban background air quality and require measurements of specific chemical species at high temporal resolution at roadside locations (i.e. more frequently than hourly at road side monitors).

Advances in exposure estimation and air quality modeling may be useful to some research approaches, depending on the type of intervention and study design. Researchers would do well to include the appropriate multi disciplinary expertise on their teams to take full advantage of such developments.

Simulation studies. Investigators are encouraged to conduct simulations to estimate and set realistic expectations for the likelihood of future studies of complex, multi-factorial health outcomes — such as cardiovascular disease or asthma — being able to detect whether changes in health outcomes occurred. It will be critical to explore in advance the sensitivity of statistical estimation and inference to model specification and time-varying confounding in any major proposed study, and quantify the expected outcomes, both in terms of exposure and health.

Methods Development

RFA 11-1 also seeks proposals for methods development, either as part of a study of specific actions taken to improve air quality or as a standalone project to develop needed statistical and epidemiologic tools or test proposed methods in an unusual population or database (e.g., a large cohort or a previously studied, dynamic population).

More robust research designs and statistical methods better suited to estimating the health effects of long-term regulatory programs and other determinants of long-term changes in health outcomes are clearly needed. However, improvements in epidemiologic and statistical methods in air pollution epidemiology, and environmental epidemiology more generally, over the past 20 years have led to advances in knowledge and methodology (Thomas 2009). The application of Bayesian hierarchical models and spatial statistics and of other geographic methods has led to better estimates of the risks of adverse health outcomes associated with long-term exposure to air pollution (Zeger et al. 2008; Krewski et al. 2009). Health outcomes research is challenging in part because it must account for both temporal and spatial patterns in the data and confounding factors (HEI Accountability Working Group 2003; van Erp and Cohen 2009). This added complexity may well require new approaches, including computationally intensive methods from other disciplines not currently employed in air pollution epidemiology.

Improvements in methods will only go so far in improving the evaluation of the public health outcomes of air quality regulations unless there are also improvements in the extent and quality of data. The limitations imposed by data availability and quality can only be overcome by a concerted effort to assemble and make widely available longitudinal data on major health outcomes, air pollution concentrations and, critically, factors that may confound or modify estimates of the effects of air quality regulations.

As the effect on health of further reductions in air pollution are likely to be small, it is important to develop a reasonably sophisticated perspective on whether future studies will have the power to detect and quantify an effect if there is one and to describe null effects with enough precision to be informative for policy purposes. Many studies will, of necessity, be retrospective, and the size of the study population will be fixed. Therefore, it will be critical to pay serious attention to the sensitivity of statistical inference to model specification and time-varying confounding.

Examples of currently needed methods development include:

- Development of techniques to use data being produced in model health tracking or surveillance systems to evaluate changes in population health status over time in relation to changes in air pollution levels due to regulatory action (e.g., changes in NAAQS). Using data from surveillance systems will likely require both a better understanding of the strengths and limitations of current methods (such as daily time-series studies) and development of new and specialized methods for the periodic analysis of health and air pollution data to evaluate changes in the health effects of air pollution over time as air quality changes. One set of opportunities for such efforts may be found in states that have been supported by the U.S. Centers for Disease Control and Prevention to develop pilot health tracking efforts (see Matte et al. 2009). Such tracking systems are generally a component of public health surveillance systems; HEI is interested in the development and demonstration of models that might be useful in applying the data from such systems in studies of air pollution and health.
- Development of techniques to better measure and integrate into health outcomes assessments other time-varying factors (e.g., changes in behavior, medical care, diet) that may also influence observed changes in health.
- Further development of approaches to improve understanding of how health outcomes are associated with specific components of air pollution mixtures, alone or in combination. Special consideration should be given to evaluation of possible synergistic effects. Health outcomes studies may provide useful information about the health effects of specific sources. In addition, they may provide information about the health effects of specific components of the mixture if they find that reductions in certain mixture components resulting from specific air quality actions are associated with reductions in health outcomes.

- Development and/or application of statistical approaches for assessing air quality interventions. Possible approaches include:
  - Syntheses of preexisting studies of actions taken to improve air quality. Such syntheses might use different approaches of combining data across studies to properly gauge the weight of the evidence. Reviews of studies and settings in which information is already available can provide information relevant to health outcomes assessment and also provide guidance as to additional information that is needed.
  - Application of formal causal models to evaluate the outcomes of actions and identify areas in which additional research is needed (e.g., Robins et al. 2000).
- Efforts to analyze and validate model-based predictions of changes in human exposure and/or health outcomes to determine how well they compare with predicted and observed effects while accounting for model uncertainty. Comparison and development of exposure models would be useful as well as validation of these exposure models. Findings from analyses that appropriately address uncertainty can provide insight into the data gaps that must be filled to make future health outcomes assessments more accurate.
- Development and validation of surrogate markers of health effects (such as medication use, symptoms, absence from school or work, or subclinical changes) that could be tracked and related to changes in air quality. Such indicators, if validated, may be useful in evaluating changes in health of populations for which mortality and hospital admissions data are not available.

WHO SHOULD APPLY?

HEI welcomes applications from academic and other public and private research institutions. Successful research proposals will in most cases require the collaboration of experts in air pollution measurement and assessment of human exposure, epidemiology, medicine, risk assessment, and biostatistics. Our experience in evaluating the first wave of health outcomes research proposals confirms the importance of the active involvement of each key discipline in the study design. Any poorly developed component may affect the disposition of the entire proposal.

Role of Government Agencies and Private Industry

Active cooperation of government regulatory and public health agencies may also be necessary for this research, but as would be the case with any research that HEI might fund, we cannot consider applications from employees of environmental regulatory agencies at the local, state, or federal levels who are responsible for developing and implementing regulations or from employees of private industries who are responsible for complying with such regulations. Such individuals may, of course, play roles as purveyors of data or other information that they collect and maintain and may be compensated by the investigators for reasonable costs entailed in providing such information. Employees of governmental agencies (such as state and local departments of public health) who do not usually have responsibility for promulgating or implementing actions to improve air quality may apply for and receive funding to conduct research under RFA 11-1.

USEFUL WEB SITES

Health Effects Institute: *www.healtheffects.org/accountability.htm*

PlanYC 2030 – Air Initiatives: *www.nyc.gov/html/planyc2030/html/plan/air.shtml*

Port of Houston – 2007 Goods Movement Air Emissions Inventory and Clean Air Strategy Plan: *www.portofhouston.com/publicrelations/environment.html*

Port of Los Angeles – Environment: *www.portoflosangeles.org/idx_environment.asp*

Port of Long Beach – Air Quality Program: *www.polb.com/environment/air/default.asp*

Port of New York and New Jersey – Clean Air Initiatives and Harbor Air Management Plan: *www.panynj.gov/about/port-initiatives.html*

Port of Oakland – Maritime Air Quality Improvement Plan: *www.portofoakland.com/environm/prog_04c.asp*

Ports of Seattle and Tacoma and Vancouver Port Authority – Northwest Ports Clean Air Strategy: *www.portoftacoma.com/Page.aspx?nid=226*

San Pedro Bay Ports – Clean Air Action Plan: *www.cleanairactionplan.org/*

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RFA 11-1: APPLICATION PROCESS AND DEADLINES

The submission and review of applications for RFA 11-1 will entail a two-stage process.

- Investigators are strongly encouraged to submit a Preliminary Application by May 18, 2011. The HEI Research Committee will discuss the preliminary applications and will provide feedback by the end of June. Investigators who do not submit a preliminary application should submit a Letter of Intent by July 13, 2011.
- All investigators should submit a Full Application by August 17, 2011. Full applications will be reviewed by a Special Review Panel before consideration by the Research Committee.

Investigators who are applying for a research project that is time-sensitive should notify HEI as soon as possible.

PRELIMINARY APPLICATION

PROJECT PLAN

The preliminary application should contain a brief description of the project plan, including proposed specific aims, study design and methods, exposure and outcome data to be accessed or collected, sources of data and data collection methods, and data analysis plans. If the proposed study will make use of available data, as well as collect additional data, sources and description of data should be included, distinguishing sources and types of data. If the proposed study will be conducted in stages or will include multiple inter-related sub-studies, the preliminary application should present plans for each sub-study separately, as well as how anticipated results would be integrated. The application should also include a discussion of the overall goal of the study and how anticipated results will contribute to the objectives of the RFA.

The preliminary application should describe how key issues pertinent to health outcomes research will be addressed, as outlined in this RFA and HEI Communication 15. Key issues include detailed estimation or modeling of the expected changes in air quality associated with the regulation; availability of air quality and health data; approaches to address weather and other confounding factors; choices of control time periods and populations; and an estimate of the power of the study to detect changes in health outcomes with a given change in air quality.

EXPERTISE AND BUDGET

The application should include specific fields of expertise among anticipated collaborators and a brief description of how their expertise would contribute to designing and conducting the study, analyzing the data and interpreting study findings. When indicated, a list of special equipment and facilities that would be available for the project should be included. The application should also include an estimate of the time and an approximate estimate of funds required to complete the study. Detailed budget pages are not required at this time.

The preliminary application should not exceed 10 pages (excluding references). Please note that the required font size is **11 point with 1-inch margins**. Brief (2-page) curricula vitae of the principal investigator and each of the co-investigators should be submitted with the application. Investigators will be informed whether or not to submit a full application after the Research Committee has considered the preliminary application.

SUBMISSION AND DEADLINE

Preliminary applications should be submitted electronically by **MAY 18, 2011**, and will be discussed at the June 2011 meeting of the Research Committee. Questions regarding applications should be directed to:

Dr. Annemoon van Erp at +1-617-488-2346
avanerp@healtheffects.org or

Dr. Aaron Cohen at 1-617-488-2325
acohen@healtheffects.org

Please send the preliminary application by email to:

Ms. Sarah Rakow
Science Administration Assistant
Health Effects Institute
101 Federal Street, Suite 500
Boston, MA 02110, USA
Tel: +1-617-488-2345
Fax: +1-617-488-2335
srakow@healtheffects.org

FULL APPLICATION

Investigators who are preparing to submit a full application should use forms **F-1 to F-10** (see list on page 35) and consult Instructions for Completing the Application found on pages 29–33. 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**. Please check our website for updates.

A full application will provide in-depth details on aspects presented in the preliminary application: specific aims, study design and methods, data to be accessed or collected, sources of data and data collection methods, data analysis, and how findings would contribute to the field. The full application should also describe in detail how key issues pertinent to health outcomes research will be addressed (see above), and include a review of the published literature that is pertinent to designing and conducting the study, and interpreting its findings.

LETTER OF INTENT

Investigators who have not submitted a preliminary application by May 18, 2011, must submit a Letter of Intent by **JULY 13, 2011**. The letter (1-2 pages) should include a synopsis of the project indicating the specific goals, the general approach to be used, and a list of all participating institutions. Please attach brief (2-page) biographical sketches of the Principal Investigator and other key personnel. The letter should be submitted electronically to Ms. Sarah Rakow at *srakow@healtheffects.org*.

SUBMISSION AND DEADLINE

Full applications should be submitted to Ms. Sarah Rakow at HEI at the address above. Full applications for RFA 11-1 must either reach the offices of the Health Effects Institute by **AUGUST 17, 2011**, or be sent by overnight air delivery service **postmarked by AUGUST 16, 2011**. Applications not meeting these conditions will not be considered. HEI will acknowledge receipt of the application.

Two printed copies (one unbound, signed original and one extra copy) of each application, plus a CD, DVD, or memory stick with all application materials are needed by HEI for the review process.

RFA 11-1: EVALUATION PROCESS FOR FULL APPLICATIONS

Full applications will be evaluated in a two-stage process: an external review followed by an internal review.

EXTERNAL REVIEW

Applications undergo a competitive evaluation of their scientific merit by an ad hoc panel of scientists selected for their expertise in relevant areas. Applications may also be sent to external scientists for additional evaluation. The panel will evaluate applications according to the following criteria:

- Relevance of the proposed research to the objectives of the RFA.
- Scientific merit of the hypothesis to be tested, the study design, exposures and outcomes to be evaluated, accessibility to existing databases of ambient air, meteorological monitoring, registries, health care utilization or other resources as appropriate, proposed methods of data collection, validation, and analysis, including adjustment for potential confounding factors, such as smoking, and development of innovative analytic methods of data analysis.
- Personnel and facilities, including:
    - Experience and competence of principal investigator, scientific staff, and collaborating investigators,
    - Extent of collaboration among investigators in pertinent fields who will contribute to the conduct of the study,
    - Adequacy of effort on the project by scientific and technical staff,
    - Adequacy and validity of existing data and data to be collected,
    - Adequacy of facilities.
- Reasonableness of the proposed cost.

The applications ranked highly by the review panel may be additionally reviewed by a statistician regarding the experimental design and analytical methods.

INTERNAL REVIEW

The internal review is conducted by the HEI Research Committee and generally focuses on the applications ranked highly by the external review panel. The review is intended to ensure that studies funded constitute a coherent program addressing the objectives of the Institute. The Research Committee makes recommendations regarding funding of studies 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 their 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 vehicle emissions. 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); applications longer than the page limit will not be considered. **No forms are necessary but please make sure to include on the first page (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. 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 the RFA booklet, including a budget, a project plan, and any additional submissions and should be prepared using forms F-1 to F-10 (see list on page 35) 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 mobile source emissions.

The full application should be sent to the following address:

Ms. Sarah Rakow
Science Administration Assistant
Health Effects Institute
101 Federal Street, Suite 500
Boston, MA 02110, USA
Tel: +1-617-488-2345
Fax: +1-617-488-2335
srakow@healtheffects.org

Two copies (one unbound, signed original and one extra copy) of each application, plus a CD, DVD, or memory stick with all application materials are needed by HEI for the review process. As with the preliminary application, the investigator should contact the Staff Scientist about the timing of submission to ensure it can be discussed at the next Research Committee meeting.

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. 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 future HEI investigators 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 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 because scientific and administrative contract negotiations may extend through a period of several months, and may result in changes in the scope or cost of the proposed study, 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. For human studies and major animal studies, a protocol and Standard Operating Procedures (SOPs) should be written before the study starts (see *Use of Human Subjects and Quality Assurance Program* below).

The contract contains a Statement of Work, which is an approved description of work to be performed in each contract year, and the budget. The scope of the research conducted should be consistent with the Statement of Work. If results suggest new directions for research, however, the contract can be amended to allow changes in the Statement of Work upon written agreement by 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 if 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 Science or Director of Finance and Administration.

STUDIES INVOLVING HUMAN SUBJECTS

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*) concerning protection of human subjects (see pages 31–33), on OMB form No. 0990-0263 (Page F-9 of HEI application forms).

If HEI decides to fund a study involving human subjects, 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:

- Application to the IRB (including supporting documentation such as the study protocol);
- 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 subject recruitment. Therefore HEI will generally not sign a contract until it has received written approval from the EPA that the study's use of human subjects 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) be provided to HEI at the time it is submitted to the IRB. HEI may propose modifications to the informed consent if it believes that the risks to the subjects are not properly represented.

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

It is the policy of HEI to require that appropriate quality assurance (QA) procedures are in place for all approved research projects that may produce data of regulatory significance; these include all human exposure studies and certain animal studies. This policy assures our sponsors and the public that the data are acquired under well-defined conditions and are reliable and traceable. 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 QA procedures consist of five components that apply to different extent to different studies: a research protocol; standard operating procedures; written records; documented data processing procedures; and data quality assessment procedures. A copy of the HEI document *Special QA Procedures* is included in Appendix C.

The Principal Investigator has the primary responsibility for development and implementation of the procedures required by HEI for QA. HEI is willing to provide some funds to support the investigator's time required to develop the protocol and the SOPs. In that case the applicant should indicate the period required for these activities and provide a separate budget.

A qualified individual selected by HEI will serve as a quality assurance officer to aid in HEI's assessment of QA activities in a study. The QA officer may conduct periodic audits to ascertain compliance with the study protocol or to examine records. 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 management of the project.

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, generally five- and ten-month reports are requested as well. In certain cases HEI science staff may indicate that submission of a 5-month report is not necessary. In the final year of the contract, the ten-month progress report is replaced by a comprehensive final report (pages 27–28).

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 actually 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, and a budget for the coming year. Progress reports are reviewed by the Research Committee and by HEI's scientific staff.

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 outside consultants. 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.

ANNUAL CONFERENCE AND OTHER MEETINGS

Each year HEI holds a conference that investigators are expected to attend. The 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. For the past several years HEI has requested that each investigator 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.

POLICY ON DATA ACCESS

Providing access to data from studies of the health effects of air pollution is an important element in ensuring credibility, especially for studies used in controversial 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 subjects 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.

FINAL REPORT

HEI has set as one of its goals to publish research reports of the highest scientific quality that will be of value to regulators, government officials, scientists, and the interested public. After a study is completed, each HEI-funded Principal Investigator prepares 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.

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. Occasionally, the Review Committee may request major changes such as additional analyses. Subsequently, the Review Committee prepares its commentary. The investigator is given an opportunity to comment on the commentary prior to publication. 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.

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 review processes. They are distributed to the motor vehicle industry, the EPA, 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. Reports that have been published are indicated in Appendix B and are available on HEI's website, *http://pubs.healtheffects.org/index.php*.

PUBLICATIONS

It is the policy of the Institute to encourage 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 under this Agreement 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 a manuscript based on all or part of the HEI-funded work when it is submitted to a peer-reviewed journal. Similarly, investigators are also required to send HEI meeting abstracts and presentations as far in advance of the meeting as possible. Article 16 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-10; see list on page 35). Applications should be typed single-spaced, within the margin limitations indicated on the forms. 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

Cost or Pricing Data: Provide adequate data and analysis to assure HEI that the proposed costs are reasonable and that adequate accounting procedures will be used. HEI has no specific limitation on the budgets of research proposals. Most of those funded to date have been within a range of $70,000 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 RFA 11-1, the budget should be prepared assuming a project start date of March 1, 2012.

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.

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 31–33).

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.

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 annual conference within the budget, since HEI will cover these costs directly. If travel is required for other purposes, 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.

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 subject to HEI's 30% cap (see below). 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).

PROJECT PLAN

(No application forms are provided but the investigator should adhere to the guidelines described below).

The Project Plan should include 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). **All sections should 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 subjects, 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 subjects and exposure groups, a calculation of statistical power, and a justification of the numbers of animals/subjects/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.

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.

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 on page 26). 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. 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

Human Subjects

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-9 of HEI application forms).

Safeguarding the rights and welfare of human subjects 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 subjects. The Health Effects Institute is responsible for ensuring that these guidelines are followed by all investigators funded by HEI.

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 subjects. 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. 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.

If the application involves human subjects, Part D of the Project Plan should include the following information:

- Identify the sources of the potential subjects, derived materials, or data. Describe the characteristics of the subject 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 subjects, prisoners, or other subjects, 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 subjects, and the methods of documenting consent. Include the consent form to be used.
- Describe potential risks to the subjects — 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 subjects, 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 subject and to society.

If HEI decides to fund a study involving human subjects, 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 subjects. In addition, HEI will need to obtain approval from EPA before subject recruitment starts, as described under *HEI Project Negotiation, Project Management, and Investigator Commitment* on pages 25–26. 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. If 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.

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 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 motor vehicle sponsors of HEI 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 must be confirmed in writing. Attach appropriate letters from each individual, confirming his or her role in the project.

Quality Assurance It is HEI's policy to apply its 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. See Appendix C for more details.

Personal Data 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-10) 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-10 are available in Portable Document and Rich Text formats.

F-1: Title Page
F-2: Table of Contents*
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: Protection of Human Subjects
F-10: Personal Data on Principal Investigator (*optional*)

* Please note that the Walter A. Rosenblith New Investigator Award has its own form F-2 NIA.
** 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.

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. At the end of 2009, the studies were at about the halfway point, with major analyses expected to be completed in 2012 and publication of results after HEI review beginning in 2013.

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 is funding 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 will use 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 plans to adapt 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 would allow 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 will test 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, plans to exploit the high correlations among multiple pollutants to characterize air pollutant mixtures emitted by a few common underlying sources. To achieve this, he will develop 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. He will test his model in two data sets collected, respectively, in Phoenix, Ariz., and Harris County, Tex. These studies began in early 2010 and are anticipated to be completed during 2012, with the reports being published in 2012-2013.

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 subjects 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 and will complete two studies funded under RFA 08-1. In one study, Stuart Batterman of the University of Chicago plans to use state-of-the-art statistical modeling techniques to conduct further analysis of the RIOPA database. His objective is to identify and characterize exposure distributions, exposures to pollutant mixtures, and dependencies between pollutants and determinants of exposure. In another study, Patrick Ryan of the University of Cincinnati will examine 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.

Completion and Publication of Air Toxics and Other Studies Initiated under Previous Plans HEI will complete the research phase and will publish the studies on PM and air toxics that were initiated under the previous Strategic Plan. During the next 18 months, HEI will publish 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 will also publish 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 will expose 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 will work with HEI to develop a common protocol and standard operating procedures. As a part of this study, HEI will encourage 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 in the early years of the new Plan, 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 research phases of these studies are complete, and they are in the midst of the HEI review and publication process. 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 will work 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.

Based on the extensive HEI-funded work on air toxics hot spots and the traffic review, HEI's Research Committee and scientific staff will convene, in the early stages of the Plan period, a multidisciplinary workshop to identify the most important needs going forward.

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 will work with its scientific committees to launch an HEI Perspective or Special Review to help 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.

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, will be completed in the next five years, and a variety of endpoints will be assessed. These end points include 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, will be evaluated only in rats. Rats will also undergo pulmonary function testing. Some of these studies are being done under separate contracts with investigators who have expertise in these areas; the exposure group at LRRI will provide the samples for testing. The final reports of ACES will be peer-reviewed intensively by the HEI Review Committee and published. In addition, we expect to plan and move forward with Phase 2, the emissions characterization of and ultimate health effects testing for 2010 engines.

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 is producing a report (expected by spring 2011) that will provide 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").

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 will focus 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 are being prepared; 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.

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 studies to be funded under the recent RFA 09-2, "Impact of Air Pollution on Infant and Children's Health in Asia");
  - 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).

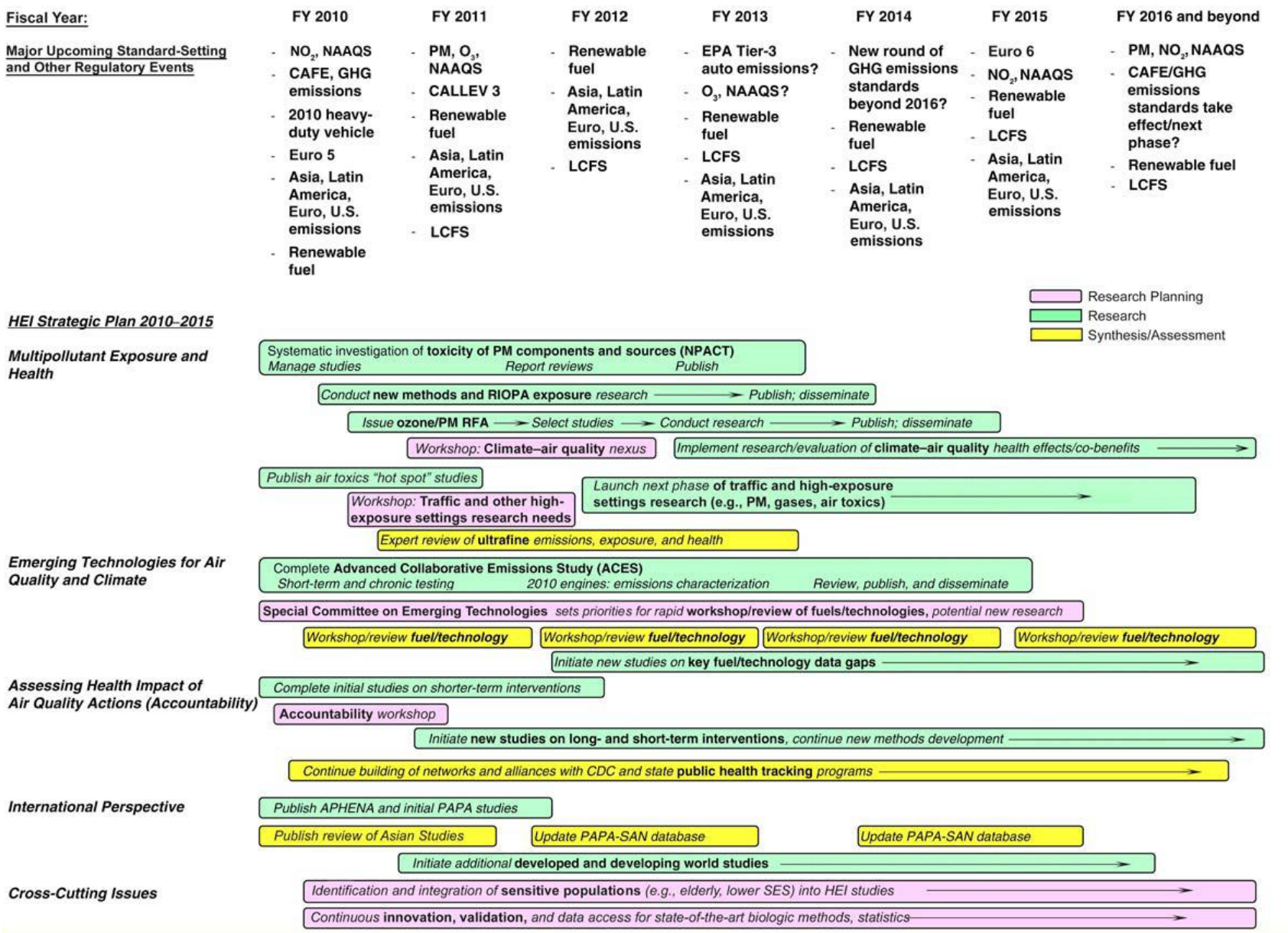
In going forward, HEI expects to continue such activities; two such types of reviews are at the top of HEI's priority list for the coming five years:

- 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); and
- Exposure to and health effects of ultrafine particles.

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 46.

[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
HEI Strategic Plan 2010–2015
Research Planning
Research
Synthesis/Assessment
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
Workshop: Traffic and other high-exposure settings research needs
Launch next phase of traffic and high-exposure settings research (e.g., PM, gases, air toxics)
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 2000–2010

RFA 10-1: CARDIOVASCULAR EFFECTS OF EXPOSURE TO LOW LEVELS OF OZONE IN THE PRESENCE OR ABSENCE OF OTHER AMBIENT POLLUTANTS
Studies under negotiation

RFPA 09-5: HEALTH EFFECTS OF AIR POLLUTION
Myoseon Jang, University of Florida
Pilot study: A Novel Exposure Method to Evaluate the Health Effects of Combustion Particulate Matter. (2011)

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. (2013)

RFIQ 09-3: STUDIES OF LONG-TERM EXPOSURE TO AIR POLLUTION AND CHRONIC CARDIO-VASCULAR AND RESPIRATORY DISEASE IN ASIA

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. (2012)
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. (2012)
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). (2012)
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. (2012)

RFA 08-2: WALTER A. ROSENBLITH NEW INVESTIGATOR AWARD

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. (2012)
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. (2012)

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. (2012)

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. (2011)

RFPA 06-4: HEALTH EFFECTS OF AIR POLLUTION
Murray Johnston, University of Delaware
Selective detection and characterization of nanoparticles from motor vehicles. (2011)
Simon Wong, University of Arizona
The molecular effects of diesel exhaust particulates on respiratory neutral endopeptidase. (Completed)

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. (2011)
Yifang Zhu, Texas A&M University
Assessing children's exposure to ultrafine particles from vehicular emissions. (2011)

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. (2012)
Daniel Conklin, University of Louisville
Effects of diesel emissions on vascular inflammation and thrombosis. (2012)
Lance Hallberg, University of Texas Medical Branch
Assessment of the genotoxicity of diesel exhaust from improved diesel engines. (2012)
Qinghua Sun, Ohio State University
Diesel exhaust exposure and cardiovascular dysfunction: ROS mechanism. (2012)
John Veranth, University of Utah
Lung cell gene transcription responses to diesel exhaust. (2012)

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: Completed; Phase 3B: 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. (Completed)
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. (2011)

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. (2011)

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. (Completed)
Qunwei Zhang, University of Louisville
Activation of endothelial cells and gene expression in lungs following exposure to ultrafine particles. (2011)

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. (2011)
Sverre Vedal, University of Washington
Integrated epidemiologic and toxicologic cardiovascular studies to identify toxic components and sources of fine PM. (2011)

RFPA 04-6: HEALTH EFFECTS OF AIR POLLUTION
Marc Baum, Oak Crest Institute
Significance of highly toxic secondary emissions from on-road vehicles. (2011)
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. (Completed)
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. (Completed)

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. (Completed)
Richard Morgenstern, Resources for the Future
Accountability assessment of the Clean Air Interstate Rule. (Completed)

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. (Completed)
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. (Completed)

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. (Completed)
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. (Completed)

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. (Completed)
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. (Completed)

RFPA 03-4: REQUEST FOR PRELIMINARY APPLICATIONS ON THE HEALTH EFFECTS OF AIR POLLUTION
David Bassett, Wayne State University
Pilot study: Pollutant exposure of an asthmatic mouse lung. (Unpublished Report)
Matthew Campen, Lovelace Respiratory Research Institute
Air pollution-induced circulatory redistribution: potential role of venoconstriction in particulate matter-associated heart failure. (Unpublished Report)
Antonio D'Alessio, University of Napoli
Pilot study: Toxicological examination of combustion-generated nanoparticles smaller than 5 nanometers. (Unpublished Report)
Andrea Ferro, Clarkson University
Pilot study: Characterization of primary and secondary particles and associated personal exposures near a major international trade bridge between the U.S. and Canada. (Unpublished Report)
Philip Hopke, Clarkson University
Pilot study: Improving source identification of carbonaceous ambient particulate matter using highly time- and composition-resolved measurements. (Unpublished Report)
Jean-Clare Seagrave, Lovelace Respiratory Research Institute
Pilot study: Consequences of chemokine binding to combustion-derived particulate matter. (Unpublished Report)
Vernon Walker, Lovelace Respiratory Research Institute

Low-dose stochastic effects of *in vivo* formation of butadiene diepoxide following *in vivo* exposure to 1,3-butadiene. (Study terminated)

RFPA 03-3: MEASURING THE HEALTH IMPACT OF ACTIONS THAT AFFECT AIR QUALITY

RFA 03-2: WALTER A. ROSENBLITH NEW INVESTIGATOR AWARD
Michael Borchers, University of Cincinnati
T-cell regulation of acrolein-induced pulmonary inflammation and epithelial cell pathology. (Report No. 146)

RFA 03-1: ASSESSING EXPOSURE TO AIR TOXICS
Eric Fujita, Desert Research Institute
Assessing exposure to air toxics. (Completed)
Roy Harrison, University of Birmingham
Measurement of modeling and exposure to air toxics and verification by biomarker. (Report No. 143)
Paul Lioy, Environmental and Occupational Health Sciences Institute
Assessing personal exposure to air toxics in Camden, New Jersey. (Completed)
Thomas Smith, Harvard School of Public Health
Air toxic hot spots in industrial parks and traffic. (Completed)
John Spengler, Harvard School of Public Health
Air toxics exposure from vehicular emissions at a U.S. border crossing. (Completed)

RFP 2003: CREATION OF AN AIR POLLUTION DATABASE
Christian Seigneur, Atmospheric and Environmental Research, Inc
Creation of an air pollution (PM) database for epidemiological studies. (Completed)

RFIQ 2003: NEW STUDIES OF THE HEALTH EFFECTS OF AIR POLLUTION IN ASIAN CITIES
Haidong Kan, Fudan University
A time-series study of ambient air pollution and daily mortality in Shanghai, China. (Report No. 154, Part 1)
Zhengmin Qian, Penn State University
Association of daily mortality with ambient particle air pollution and effect modification by extremely hot weather in Wuhan, China. (Report No. 154, Part 2)
Nuntavarn Vichit-Vadakan, Thammasat University
Estimating the mortality effects of air pollution in Bangkok, Thailand. (Report No. 154, Part 3)
Chit-Ming Wong, University of Hong Kong
Interaction between air pollution and respiratory viruses: time-series studies for daily mortality and hospital admissions. (Report No. 154, Part 4)
Chit-Ming Wong on behalf of PAPA teams
Public Health and Air Pollution in Asia (PAPA): A multi-city study for short-term effects of air pollution on mortality. (Report No. 154, Part 5)

RFPA 02-3: REQUEST FOR PRELIMINARY APPLICATIONS ON THE HEALTH EFFECTS OF AIR POLLUTION
Marc Baum, Oak Crest Institute
Pilot study: Significance of highly toxic organo-nitrogen emissions from on-road vehicles. (Unpublished Report)
Lester Kobzik, Harvard School of Public Health
Pilot study: Oxidative stress and cardiac dysfunction in animals exposed to environmental oxidants. (Unpublished Report)
Christine Nadziejko, New York University
Pilot study: Role of sensory irritant receptors and particle-phase organics in the toxicity of particulate matter. (Unpublished Report)
Jan Powell, University of Maryland
Pilot study: Synergistic effects of endotoxin and vehicle emissions. (Unpublished Report)

RFA 02-2: WALTER A. ROSENBLITH NEW INVESTIGATOR AWARD
James Schauer, University of Wisconsin
Source apportionment and speciation of particulate matter for exposure and health studies. (Report No. 153)

RFA 02-1: MEASURING THE HEALTH IMPACTS OF ACTIONS THAT IMPROVE AIR QUALITY

Douglas Dockery, Harvard School of Public Health
Effects of air pollution control on mortality and hospital emissions in Ireland. (Completed)

Annette Peters, GSF-Forschungszentrum für Umwelt und Gesundheit
Improved air quality and its influences on short-term health effects in Erfurt, Eastern Germany. (Report No. 137)

RFPA 00-3: HEALTH EFFECTS OF AIR POLLUTION

Thomas Cahill (Judith Charles), University of California at Davis
Exposure of tollbooth attendants to acrolein and other toxic carbonyls in the San Francisco Bay area. (Report No. 149)

Kevin Harrod, Lovelace Respiratory Research Institute
Mechanisms of diesel engine emission-induced susceptibility to respiratory viral infection. (Unpublished Report)

RFA 00-2: WALTER A. ROSENBLITH NEW INVESTIGATOR AWARD

Quanxin Meng, Battelle Toxicology Northwest
Mutagenicity of stereochemical configurations of 1,3-butadiene epoxy metabolites in human cells. (Report No. 150)

RFA 00-1: EFFECTS OF DIESEL EXHAUST AND OTHER PARTICLES ON THE EXACERBATION OF ASTHMA AND OTHER ALLERGIC DISEASES

Marc Riedl (David Diaz-Sanchez), Los Amigos Research and Education Institute
Exacerbation of allergic inflammation in the lower respiratory tract by diesel exhaust particles. (Completed)

Jonathan Grigg, University of Leicester
Black-pigmented material in airway macrophages from healthy children: association with lung function and modeled PM_{10}. (Report No. 134)

Jack Harkema, Michigan State University
Fine airborne particles and allergic diseases. (Report No. 145)

George Thurston, New York University
Pilot study: Children's asthma incidence and personal exposures to diesel particles and traffic in New York City. (Completed)

Junfeng Zhang, Environmental and Occupational Health Sciences Institute
Health effects of diesel exhaust in asthmatic patients: a real-world study in a London street. (Report No. 138)

APPENDIX C: HEI SPECIAL QUALITY ASSURANCE PROCEDURES

I. POLICY STATEMENT

It is the policy of the Health Effects Institute to utilize special quality assurance (QA) procedures for research projects that may produce data of regulatory significance. These procedures augment the QA/QC procedures applied to all HEI studies and provide assurance that data are collected under defined conditions and are reliable and traceable. This will aid in assuring that conclusions drawn from the data are scientifically valid. 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.

Quality assurance is achieved through six basic components:

A. Use of a written protocol

B. Use of written standard operating procedures

C. Involvement of qualified personnel

D. Maintenance of written records

E. Use of appropriate data processing techniques

F. Use of quality control procedures for all data collected

In addition to QA components addressed in this document, it is essential that the appropriate institutional review boards approve the research plans for human studies.

II. QUALITY ASSURANCE COMPONENTS

A. *A written research protocol*, to be reviewed and approved by HEI, will define 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
2. Background of problem being addressed
3. A statement of the problem being addressed
4. Expected results and their significance
5. Description of all experiments to be conducted with reference to a particular standard operating procedure when appropriate (see Section B)
6. Subject selection procedures to be used, including inclusion and exclusion criteria (when applicable)
7. Details of the acceptance and testing of chemicals and reagents if they are to be used
8. Personnel needed to accomplish the research (see Section C)
9. Description of data to be collected
10. Methods of data processing (see Section E)
11. Quality control procedures to be used (see Section F)
12. Safety precautions needed

Any changes to the original protocol shall be made in writing by preparing an amendment to the protocol. All amendments must be approved by HEI.

B. *Written standard operating procedures* (SOPs) 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.

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.

Standard operating procedures will be prepared in document control format. Each SOP will be uniquely identified. SOPs will be updated as needed, and revised SOPs will also be uniquely identified and dated. There will be copies of all SOPs readily available for reference by individuals as needed. They will generally be found in the immediate area where work is in progress. An up-to-date record of all approved SOPs will be maintained.

Deviations from SOPs will be justified and documented. The degree of adherence to the SOPs may be determined during periodic audits.

Standard operating procedures will be:

1. Adequate to establish traceability of standards, instrumentation, samples and data;
2. Simple, so that a user with a basic education, and experience or training can properly use them;
3. Complete enough so that individuals can follow the directions in a stepwise manner through the sampling, analysis, and data handling;
4. Consistent with sound scientific principles;
5. Consistent with current regulations and in general conformity with the intent of Good Laboratory Practice guidelines;
6. Consistent with the instrument manufacturer's specific instruction manuals.

To accomplish these objectives, standard operating procedures will be developed for procedures and equipment including the following as may be appropriate:

1. Laboratory instruments
2. Subject care, handling, treatment, and transportation
3. Sampling procedures
4. Analytical procedures
5. Special precautions for samples and specimens of all types that are collected, such as holding times and protection from heat, light, reactivity, and combustibility
6. Federal reference, equivalent, and alternate test procedures
7. Instrumentation selection and use
8. Collaboration and standardization procedures
9. Preventive and remedial maintenance
10. Replicate sampling and analysis
11. Blind and spiked samples
12. Quality control procedures
13. Precision, accuracy, completeness, representativeness, and comparability
14. Sample and specimen custody, handling and storage procedures
15. Sample transportation
16. Data handling and evaluation procedures
17. Automatic data processing procedures
18. Documentation and document control

C. *Qualified personnel* will conduct the proposed research. The qualifications of all participating individuals will be documented in resumes that will be maintained as a part of the permanent record of the project.

D. *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, at not less than biweekly intervals, 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. ***Documented procedures*** will be used to assure the integrity and appropriateness of data processing procedures. Data processing includes all manipulations performed on raw, (i.e. "as collected") information to change its form of expression, its location, or its quality. This includes data collection, validation, storage, transfer, reduction, and analysis.

1. Collection

   The protocol and SOPs will address both manually and electronically collected data. The internal checks that must be used to ensure suitable quality in the data collection process will be identified.

2. Validation

   Validation of raw data will also be addressed in the protocol and SOPs. The validation in process may include many forms of manual or computerized checks, but it clearly involves specified criteria.

3. Storage

   Data storage involves keeping the data in such a way that they are not degraded or compromised, and that all values will be uniquely identified. At every stage of data processing at which a "permanent" collection of data is stored, there will be a physically separate copy for purposes of integrity and security.

4. Transfer

   The protocol will address quality assurance procedures that will be used to characterize data transfer, error rates, and how information loss is minimized in the transfer.

5. Reduction

   Data reduction includes all processes that change either the value or number of data items, i.e., the original data set from which it is generated cannot be recovered from it. This process is distinct from data transfer in that it entails a reduction in the size of the data set and an associated loss of information.

   Validation of the reduction process will be appropriate to the level of effort involved. When a computer is used to process large quantities of data, reference to the specific program documentation and data base documentation will be provided. Each type of processing should provide sufficient information to allow a reviewer to check the validity of the conversion process against a current methodology.

6. Data 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). The protocol will address the specific statistical procedures to be used, the reliability of computations, appropriateness of the models as a framework for investigating the study questions and robustness of statistical procedure to model inaccuracies.

F. ***Quality control procedures*** will be included, to the extent possible, in the protocol and SOPs to address the quality of all data generated and processed and to assess the data for precision, accuracy, representativeness, comparability, and completeness. The aspects of data quality are:

1. Precision

   Each SOP concerned with measurement will contain a mechanism for displaying the reproducibility of the measurement process. Examples of activities to assess precision are:

   a. Replicate samples

      Replicate sample data shall be within predetermined acceptance limits.

   b. Instrumental checks

      Each measurement device shall have routine checks done to demonstrate that variables are within predetermined acceptance limits.

   Examples of checks include:

   (1) Zero and span
   (2) Noise levels
   (3) Drift
   (4) Flow rate
   (5) Linearity

2. Accuracy

Each SOP concerned with measurements will contain a mechanism for showing the limits of accuracy for reported data. This will be accomplished with the following procedures:

a. Traceability of instrumentation

Each instrument used to produce data critical to the quality of project output will be assigned a unique identification number or be identified uniquely in another way. The specific instrument used, where and when used, maintenance performed, and the equipment and standards used for calibrations will be identified.

b. Traceability of standards

Each standard and each measurement device will be calibrated against a standard of known and higher accuracy. The standards used will be defined in the Protocol.

c. Traceability of samples

When samples are extracted from the test system, each sample will be assigned a unique identification number or be identified uniquely in another way. Documentation shall identify sampling time, place, and action taken on each sample.

d. Traceability of data

Data will be documented to allow complete reconstruction, from initial records through data storage system retrieval and final reporting of data in various progress reports and publications.

e. Methodology

Methodology if available, Federal reference, equivalent, or approved alternate test methods will be used.

f. Reference or spiked samples

Recoveries will be within predetermined acceptance limits, as defined in the SOPs and Protocol.

3. Representativeness

Each sampling SOP will contain procedures to ensure and document that each sample collected represents the media sampled as far as is possible. This will involve detailed consideration of the total system being sampled and its manipulation in relationship to the validity of raw data finally recorded.

Parameters used for this aspect of data quality will be specified (e.g., storage temperature) and recorded as part of the raw data.

4. Comparability

Each measured SOP will contain procedures to assure the comparability of data.

Examples are:

a. Consistency of reporting units

b. Standardized setting, sampling, and analysis

c. Standardized data format

III. ROLES OF INSTITUTIONS AND INDIVIDUALS IN ACHIEVING QUALITY ASSURANCE

A. Health Effects Institute

Dr. Rashid Shaikh, Director of Science, has overall responsibility for implementation and oversight of the HEI Special Quality Assurance Procedures. Members of the HEI Research Committee, consultants to it, and HEI staff members shall serve as facilitators of the research. This shall include aid in the identification of the experimental objectives and the methodologies by which the objectives are to be achieved. These individuals may offer suggestions to facilitate the conduct of the research. They may periodically critique the research in progress.

For each study, Dr. Shaikh will approve, on behalf of HEI, the protocol and amendments to it and, if appropriate, the SOPs.

B. Project Personnel

1. Principal Investigator

The Principal Investigator has the primary responsibility for specifying the detailed experimental objectives and the research methodologies by which the objectives will be achieved. He or she has the primary responsibility for the preparation of the protocol and all standard operating procedures and shall review and approve them by signing them.

The Principal Investigator has the responsibility for the actual conduct of the research according 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 has the responsibility for assuring that the research is conducted with qualified personnel and in accordance with this quality assurance plan.

2. Professional personnel

The professional personnel associated with each center have the responsibility for carrying out their aspects of the research according to this quality assurance plan. They are expected to be knowledgeable of the protocol and the SOPs being used in their research. They have the responsibility for assuring that personnel working under their supervision carry out their activities according to approved SOPs.

3. Technical and supporting personnel

The technical and other supporting personnel at each research institution shall have the responsibility for carrying out their assigned activities in accordance with this quality assurance plan. They should have a detailed knowledge of the SOPs used in the conduct of their research activities.

C. Special QA Oversight

If not provided by the institute at which the research project is being carried out, HEI shall engage a qualified individual to serve as Quality Assurance Officer for the project. This individual shall report to HEI's Director of Science and be responsible for overseeing the implementation of this quality assurance plan. The QA Officer shall review the protocol and, when appropriate, the SOPs, and advise the HEI staff if modifications are necessary to assure their QA adequacy. The QA Officer shall maintain signed copies of the protocol and all SOPs.

The Special QA Officer 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. At the conclusion of each audit, the QA Officer shall provide a verbal summary to the Principal Investigator of significant findings that need to be addressed. The QA Officer shall also prepare 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 the Principal Investigator. If corrective action is required, the Principal Investigator shall see that such action is taken and return the summary to the HEI project manager with a copy to the QA Officer noting the action 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 Officer shall maintain a log of all audits indicating for each audit: the date conducted, participating personnel, and the nature of the audit.

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 subjects 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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