Request for Applications

HEALTH EFFECTS INSTITUTE

FEBRUARY 2010

Winter 2010 Research Agenda

RFA 10-1 Cardiovascular Effects of Exposure to Low Levels of Ozone in the Presence or Absence of Other Ambient Pollutants

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.

THE HEALTH EFFECTS INSTITUTE – WINTER 2010 RESEARCH AGENDA

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INTRODUCTION

This booklet contains the Winter 2010 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 10-1: CARDIOVASCULAR EFFECTS OF EXPOSURE TO LOW LEVELS OF OZONE IN THE PRESENCE OR ABSENCE OF OTHER AMBIENT POLLUTANTS

HEI is issuing this RFA to fill an important gap in our understanding of health effects of air pollutants, namely the effect of exposures to low levels of ozone on the human cardiovascular system and the influence of other ambient air pollutants on such effects. The RFA focuses on effects on the cardiovascular system of low-level exposure to ozone, in the presence and absence of an ambient multi-pollutant mix, in a susceptible group; however, effects on the respiratory system are also of interest.

Two types of studies are sought to evaluate cardiovascular and respiratory effects in healthy human volunteers, aged 55 and above.

- Phase 1: Studies in volunteers exposed to ozone alone, at concentrations between 60 and 100 ppb, in a controlled laboratory setting.
- Phase 2: Studies in volunteers exposed to real-world ambient air pollution at sites with ozone concentrations comparable to those used in Phase 1.

Interested scientists can apply to Phase 1, Phase 2, or both.

DEADLINES

Letters of Intent are due on March 29, 2010.

Applications are due on May 6, 2010.

Twelve printed copies and one electronic copy of each application are needed for HEI's review process.

REQUEST FOR PRELIMNARY APPLICATIONS

HEI will continue to accept preliminary applications through the end of the year. Please refer to the Fall 2009 Research Program for information on how to apply.

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 19-22.

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 21-22.

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 will be issuing a new five-year plan, the *HEI Strategic Plan for Understanding Health Effects of Air Pollution 2010–2015*, which will describe 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 Plan describes four priority areas:

- **Multi-Pollutant Research on Exposure, Epidemiology, and Toxicology**. HEI will move to initiate new research to test the effects of ozone and PM on the cardiovascular system (RFA expected to be issued in 2010). 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's review of the literature on the health effects of exposure to traffic (HEI Special Report 17, 2009 in press).

- **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 (Accountability)**. HEI plans to hold a workshop in December 2009 to identify challenges and opportunities for further research on accountability. Key recommendations are expected to be included in the final version of the Strategic Plan (to be issued in March 2010) and in workshop proceedings (to be published in 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); systematic efforts to assess actions aimed at reducing exposure of susceptible populations; and the potential for additional studies of interventions designed to significantly improve air quality for specific major events (e.g. Olympic Games).

- **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.

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.

REQUEST FOR APPLICATIONS (RFA) 10-1: Cardiovascular Effects of Exposure to Low Levels of Ozone in the Presence of Other Ambient Pollutants

HEI is issuing this RFA to fill an important gap in our understanding of health effects of air pollutants, namely the effect of exposures to low levels of ozone on the human cardiovascular system and the influence of other ambient air pollutants on such effects. Although responses to near-ambient level exposures to ozone have been studied previously, most studies have focused on respiratory effects in healthy young people. This RFA focuses on effects on the cardiovascular system of low-level exposure to ozone, in the presence and absence of an ambient multi-pollutant mix, in a susceptible group.

Studies under this RFA will be divided into two phases. Phase I will focus on cardiovascular responses in people exposed to ozone near ambient levels in a controlled laboratory setting. The subjects will be drawn from a subgroup of the population considered at higher risk for adverse cardiovascular responses to air pollution: people aged 55 and above. Phase II will focus on cardiovascular responses in the same subgroup of the population, but exposed in ambient settings to ozone at concentrations similar to those studied in the laboratory but in the presence of other air pollutants – among which particulate matter (PM) is of particular interest. The protocol used for Phase II studies will be as similar to the Phase I protocol as possible to maximize comparability of results between the two phases.

The studies under both phases of this RFA are envisioned as multicenter studies, in which the selected teams will use a common protocol to evaluate a common set of endpoints. A multicenter design offers several advantages: for Phase I, it will allow for larger numbers of subjects to be studied in a shorter period of time; for Phase II, it will also capture the effects of variations in the composition of pollutants – especially PM. Investigator teams may apply for funding for either Phase I or Phase II, or both.

BACKGROUND

Ozone is a photochemical oxidant formed in the lower atmosphere, in the presence of sunlight, through complex photochemical reactions among pollutants created from anthropogenic and natural sources. Human exposure to increased levels of ozone produces adverse respiratory and cardiovascular responses and may also have other effects. Ozone is one of the six criteria pollutants regulated by the U.S. Environmental Protection Agency (EPA) under the Clean Air Act. The literature on the health effects of ozone has been extensively and recently reviewed by both the National Research Council (NRC) (2008) and the EPA (US EPA 2006 and 2007).

HEI is issuing this RFA in an attempt to fill an important gap in knowledge, namely the health effects of exposure to low levels of ozone – with and without other air pollutants – on the cardiovascular system. Certain aspects, particularly pulmonary effects, of ozone are well documented. The NRC (2008) committee concluded "from its review of the health-based evidence that short-term exposure to ambient ozone is likely to contribute to premature deaths." Further elaborating on this conclusion, the committee noted that:

"Human chamber and toxicologic studies have yielded strong evidence indicating that short-term exposure to ozone can exacerbate lung conditions, causing illness and hospitalization, and can potentially lead to death. The available evidence on ozone exposure and exacerbation of heart conditions, which is less abundant, points to another concern. Epidemiologic studies have also found that exposure to ozone is associated with adverse lung and heart effects."

In March 2008 the EPA published a final rule for the National Ambient Air Quality Standards for ozone, setting both the "primary" (for the protection of human health) and "secondary" (for the protection of the environment) standards to an identical level at 0.075 ppm. Late last year, the agency undertook a reconsideration of the ozone standards; this resulted in a proposed revision, issued on January 6, 2010. The current proposal would further strengthen the standards, setting the standard for health protection to a level within the range of 0.060 – 0.070 ppm, measured over 8 hours, and establishing a distinct cumulative, seasonal form for the secondary standard, set at a proposed level within the range of 7-15 ppm-hours. The agency intends to finalize its rule by August, 31, 2010.

One of the health studies that played a pivotal role in the EPA's standard setting process was a controlled human exposure study published by Adams (2006). He exposed 30 healthy young male and female volunteers to 0.04 to 0.08 ppm ozone for 6.6 hours with moderate, nearly continuous, exercise (minute ventilation [V_E] of 40 L/min) and used different ozone exposure profiles (square-wave and triangular). The effects of exposure at 0.08 ppm showed similar decrements in pulmonary function (FEV_1 decreased 6-8%) to those reported in previous studies (e.g., Adams

2003, Horstman et al 1990). At the lower ozone exposure levels, 0.04 and 0.06 ppm, which had not been used in earlier controlled exposure studies, Adams reported that he could not discern a statistically significant effect (Adams 2006). Investigators from the EPA, however, re-analyzed data from Adams' 2006 study using alternative statistical methods and reported that exposure to 0.06 ppm ozone resulted in a statistically significant decrement in FEV_1 (2.85%) (Brown et al 2008). More recently, Schlegele et al (2009) tested young, healthy volunteers using a similar protocol to that used by Adams (2006) and reported that inhalation of ozone at 0.07 ppm and higher, but not 0.06 ppm, induces a statistically significant decrement in FEV_1.

In summary, these studies suggest that healthy subjects in their 20s, exercising for relatively long periods of time (thus simulating a healthy worker laboring heavily outdoors in the summer), show a dose-related decrease in FEV_1 when exposed to ozone at levels $\geq$ 0.07 ppm; the results of studies employing exposure at 0.06 ppm of ozone are inconsistent.

The studies cited above did not focus on effects of ozone on the cardiovascular system and the effects of ozone exposure on the cardiovascular system at such low levels are not known. A few investigators, however, have examined the cardiovascular effects of ozone at considerably higher levels. For example, in healthy and hypertensive volunteers exposed to 0.3 ppm ozone for 3 hours, Gong et al (1998) did not find statistically significant differences between the healthy and hypertensive groups following ozone exposure; however, they reported finding larger pre-exposure to post-exposure changes in heart rate and pressure-product rate for ozone compared to filtered air. They interpreted these findings as suggesting that ozone exposure can increase myocardial work and impair pulmonary gas exchange. This study was done on a relatively small number of subjects, the subjects were older, with average age at 53 for the hypertensive group and 44 for the healthy group, and they exercised intermittently during exposure. Thus, our knowledge regarding the effects of low (near ambient) levels of ozone exposure on the human cardiovascular system is very limited.

Another important facet of these studies is that volunteers were exposed to ozone alone. Though such studies have provided useful information, ozone-alone exposure does not reflect the complex mixture of pollutants to which people are exposed. However, the U.S. Clean Air Act and most existing air quality guidelines and standards – as well as scientific studies – focus on single pollutants in isolation. The study and regulation of mixtures is challenging, and EPA and other organizations – including HEI – are conducting research in this critical area. This RFA is a part of a broader multi-pollutant research strategy being implemented by HEI.

The concurrent effects of another criteria air pollutant, PM, are of particular interest in this context. Epidemiologic studies have suggested that exposure to ozone and PM is associated with increased cardiopulmonary mortality (e.g. Samet et al 2000) and morbidity (e.g. Schwartz 1999), but only a few studies have examined the short-term cardiovascular effects in humans of controlled exposure to a combination of ozone and PM. In one study, 25 healthy adults were exposed for 2 hours to approximately 150 $\mu g/m^3$ concentrated ambient particles (CAPs, fine particles concentrated from the ambient air in Toronto, Canada) and 0.12 ppm ozone or a filtered air control (Brook et al 2002). Measurements made immediately after the exposure indicated that, compared to the filtered air control, participants exposed to ozone plus CAPs had significant constriction of the brachial artery as measured by high-resolution vascular ultrasonography. No changes were observed in endothelial-dependent flow-mediated dilatation, endothelial-independent nitroglycerin-mediated dilatation, or blood pressure. In a subsequent study by the same group (Urch et al 2005), healthy adults exposed for 2 hours to 150 $\mu g/m^3$ $PM_{2.5}$ CAPs in combination with 0.12 ppm ozone showed a 9.3% increase in diastolic blood pressure measured just before the end of the exposure period. In a recent study (Power et al 2008), five asthmatic adults were exposed for 4 hours to either laboratory-generated particles of carbon and ammonium nitrate, a combination of ozone and particles, or a filtered air control. ECG readings made before and after the exposures suggested that, compared to the filtered air control, exposure to the combination of carbon and ammonium nitrate particles plus ozone was associated significantly with decreased heart rate variability (HRV). Exposure to particles alone did not affect HRV. Two studies of sequential exposure of healthy adults to ozone and diesel exhaust have reported that exposure to both pollutants enhances inflammatory responses in the airways compared to the effects of either exposure alone (Bosson et al 2007, 2008).

Taken together, these findings suggest that short-term exposure to ozone, in the presence of high levels of PM, can affect cardiovascular responses. Additionally, as mentioned above, there is a large body of epidemiological evidence suggesting an association between PM exposure and cardiovascular mortality and morbidity.

RATIONALE AND GOALS OF RFA 10-1

HEI is interested in research on the effect of exposures to ozone on the human cardiovascular system and the influence of other air pollutants on such effects. Studies will be conducted in two phases:

- Phase I will focus on investigation of the cardiovascular effects of ozone at near ambient levels in the laboratory: human volunteers, ages 55 to 70 with no clinically diagnosed cardiovascular disease, will undergo controlled, chamber exposure to ozone, at concentrations of 0.06 and 0.10 ppm, while exercising intermittently. Cardiovascular (primary endpoints) and other physiological responses (secondary endpoints, such as pulmonary function and inflammation) will be measured.

- Phase II studies will be conducted at sites proposed by investigator teams, where ozone concentrations are comparable to the levels used in the Phase I laboratory studies, but in the presence of other ambient pollutants among which PM is of special interest. The subject selection criteria and study protocol in Phase II will be as similar as possible to those employed in Phase I to maximize comparability between the two phases

KEY FEATURES OF PHASE I AND PHASE II STUDY DESIGNS

HEI considers the following features of the study design critical; however, investigators are encouraged to elaborate on and refine them. After the selection process is completed, HEI will work with the selected teams to define the most appropriate methods and develop protocols that will be followed by all the investigator teams.

PHASE I:

- Study Population

  Males and females, ages 55-70 years, non-smokers, with no clinically diagnosed cardiovascular or pulmonary disease or diabetes. To ensure the safety of participants in the study, strict compliance with institutional IRB and HHS human subjects regulations [as specified in 45 CFR Part 46] will be required. Investigators should propose criteria for inclusion and exclusion of subjects from the study. A normal baseline ECG, read by a cardiologist, will be required before a subject is enrolled in the study. Information on each subject's use of medications will be collected. Subjects taking beta-blockers or any other medications known to interfere with response of the cardiovascular system will be excluded; however, subjects with stable and well-managed hypertension may be eligible.

- Exposure
  - At least three separate exposures for each subject: filtered air and laboratory-generated O_3 at 0.06 and 0.10 ppm.
  - Each exposure will be two to three hours long, with intermittent exercise (minute ventilation [V_E] of 15-20 L/min)
  - Exposures will be performed in appropriate chamber facilities, without facemasks
  - To understand the likely ambient exposures of the subjects prior to the laboratory experiment, information on ambient levels of O_3, NO_2, PM and other relevant air pollutants measured by the investigator team at or near the exposure site will be required. Alternatively, data from a local monitoring station will be acceptable if the investigator can justify that such data are representative of urban ambient conditions.

- Endpoints

  HEI asks investigators to propose appropriate endpoints for studying the cardiovascular pathophysiology of responses to ozone; relevance of the selected endpoints with respect to clinical indications of disease should be discussed. The endpoints proposed for Phase I studies should also be readily measurable in Phase II studies. Some examples of the endpoints that may be studied are listed below, but this is not meant to be a prescriptive or an exhaustive list:

  - ECG Parameters (e.g., Holter monitoring, ischemia, arrhythmia, heart rate variability, repolarization)
  - Vascular function and endothelial dysfunction
  - Markers of systemic inflammation and oxidative stress
  - Thrombosis and clotting parameters
  - Pulmonary function, including spirometry, and markers of pulmonary inflammation and oxidative stress
  - In addition to the above endpoints, HEI encourages investigators to supplement them with promising, newer methods or analytical techniques, such as genomic or proteomic approaches. The inclusion of any such methods should be carefully justified.

PHASE II

- Study population

  Study Population: inclusion criteria and safety features (IRB review, baseline ECG, etc) will be the same as for Phase I.

- Site Selection

  The selection of appropriate site(s) is a very critical aspect of Phase II studies; applicants may use the following as a guide in proposing a site or sites for their study. The suitability of the selected site should be demonstrated by providing data from outdoor air monitoring databases to meet the objectives of this study.

  - Any environment where the hourly average ozone levels are expected to be in the range of 0.06 to 0.10 ppm (or higher). HEI is open to considering various study designs, including studies performed using a mobile laboratory or a chamber where outdoor air can be used for exposures. Studies may need to be planned during those parts of the year and hours of the day when ozone levels are near their peak and within a temperature and humidity range that is suitable for exercise.
  - Among the other pollutants present at exposure sites in addition to ozone, HEI is particularly interested in investigating the effects of co-exposure to PM. Questions related to the variability in PM – such as ambient concentrations and composition, including geographic variations and seasonal changes – are of great interest. HEI welcomes proposals that seek to investigate one or more of these variables in Phase II and asks the investigators to provide justification for their approach. However, because addressing such issues may make the study more complex and difficult, HEI will not penalize applicants who do not address the issues related to PM variability.
  - Should the selected site not be at or near sea level, investigators should address the issue of how responses may be affected by elevation above sea level.

- Exposure

  - Investigators are asked to specify how many separate exposures will be conducted for each subject.
  - Each exposure will be two- to three-hours long, with intermittent exercise (minute ventilation [V_E] of 15-20 L/min).
  - Investigators should have the capability – or collaborate with a group that has such capability – to measure the levels of gaseous and particulate air pollutants within ~100 meters of where the exposures are being conducted. Alternatively, information on individual pollutants available from a nearby monitoring site representative of air pollutant levels at the exposure site may be acceptable. A list of pollutants whose levels will be monitored should be provided.

- Endpoints

  - As for Phase I, HEI asks investigators to propose endpoints in Phase II that are most relevant to studying the cardiovascular pathophysiology of responses to ozone and PM exposures; secondary endpoints for effects on pulmonary function and inflammation – as discussed above – should also be proposed. Investigators may use the list provided in the description of Phase I as a starting point and provide justification for the endpoints they select. Note that HEI will work with the investigator teams selected for Phases I and II to ensure that the same set of endpoints is studied in both phases, as far as possible.

Investigator teams may apply for either or both phases of this RFA; as described in subsequent sections, investigators are asked to propose their own protocols to carry out the study and plans for data analysis. For Phase II, investigator teams must provide justification for the selection of the study site(s) and, based on available monitoring data, an indication of the levels of ozone and PM expected at the site.

HEI anticipates that Phases I and II will be conducted as multicenter studies at two or more sites in different regions of North America or Europe, so that the number of subjects studied can be optimized and the effects of different ambient environments can be investigated. To ensure that all teams use study design features and protocols that yield comparable results, HEI will select teams for Phases I and II at the same time. Before the studies in either phase are launched, HEI will work with the selected teams and outside experts to develop specific, detailed protocols, standard operating procedures including quality assurance-quality control procedures and data analysis plans that will be used by *all* investigators. As details of the protocols are discussed, HEI may decide to perform

certain assays at a central laboratory that specializes in that area, but investigators should indicate how and where samples collected in their own study will be analyzed. HEI will also work with the investigator teams to schedule the beginning of each phase of the study. In addition, it is anticipated that data collected at local sites will be sent to a central data management and analysis center, designated by HEI, where pooled analysis of the data will be performed as specified in the protocol. Individual teams will have access and the rights to analyze their own data. In view of the expected multicenter nature of this research, the timing and process of publication of this work in peer-review publication(s) and at scientific meetings will be discussed and decided upon by the selected teams and HEI before the studies begin. (Note: Submission of progress reports and final reports by HEI is expected to follow the normal HEI process, as described on pages 20-22).

HOW TO APPLY

HEI seeks applications from teams with a range of expertise in the various aspects of the two phases outlined above, including – but not limited to – human studies (chamber or field or both), cardiac and/or pulmonary medicine, air sampling and pollutant characterization, biostatistics, and adherence to stringent QA/QC procedures. Members of a team need not be from the same institution.

Investigators may apply for Phase I, Phase II, or both. If they apply for both phases, they must submit separate applications for each phase.

Instructions for preparing the application are provided in Instructions for Completing the Application Process (pages 23-27). In addition, full applications need to include the following information in Section A of the Project Plan (see page 24):

1. Names and affiliations of key team members, a description of their role in the project, and evidence of the ability of team members to work together as a group. The application should document that key team members will be able to commit adequate levels of effort to the project to complete it within the timeframe of the study.

2. A description of the team members' experience in:

- Designing and conducting controlled, inhalation studies to evaluate the health effects of either ozone or other gaseous compounds in humans [Phase I applicants];
- Working with subjects in the field [Phase II applicants];
- Studying cardiovascular and pulmonary indicators of health effects and collecting information on a variety of cardiovascular and pulmonary function endpoints, and obtain samples for inflammatory measurements, in laboratory (Phase I) or under field conditions (Phase II);
- Applying statistical methods to the analysis of data from human clinical or epidemiological studies of the health effects of air pollutants;
- Characterizing gaseous and particulate air pollutants; and
- Working with stringent QA/QC procedures and with human subjects with full measures for safety and welfare of the subjects.

3. Details of the facilities and equipment to which the investigators' team will have ready access during the course of this study. The application should document that adequate support personnel and other resources will be available to perform the proposed study, and that team members will be able to commit adequate levels of effort to the project to complete it within the timeframe of the study.

4. The plan for subject recruitment and the number of subjects to be recruited. Respondents to this RFA need to demonstrate access to and ability to recruit sufficient numbers of males and females (in roughly equal numbers), ages 55-70, non-smokers, with no clinically diagnosed cardiovascular or pulmonary disease or diabetes. Information on the use of any medications must be obtained.

5. For applicants for Phase II, details of the proposed exposure site(s), including preliminary data on the anticipated levels of ozone and PM.

6. A proposed time-line for the study

FUNDING

HEI expects to fund up to three studies for each Phase of this RFA, with an anticipated total funding of up to $5 million.

QUESTIONS

Inquiries concerning the application and evaluation processes should be directed to Drs. Maria Costantini (617.488.2302, mcostantini@healtheffects.org) or Rashid Shaikh (617.488.2301, rshaikh@healtheffects.org).

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RFA 10-1: APPLICATION PROCESS AND DEADLINES

LETTER OF INTENT

Although not required as part of the application process, applicants are encouraged to submit a one-page Letter of Intent summarizing the proposed project prior to submitting an application. HEI requests Letters of Intent in order to organize the application review process.

The Letter of Intent should specify the general approach to be used and where study will be conducted and provide the names and affiliation of the principal investigator and the co-investigators.

If an applicant misses the deadline for Letters of Intent we urge him/her to send us a late Letter of Intent.

Deadline for Letters of Intent: The Letter of Intent should be sent no later than **MARCH 29, 2010**, by or email to Sarah Rakow at *srakow@healtheffects.org*.

FULL APPLICATION

Full applications must be submitted on the forms **F-1 to F-10** (see list on page 29 of this booklet) that can be found on our website at *www.healtheffects.org/funding.htm*. Investigators applying to both Phase1 and Phase 2, should submit two separate applications.

Investigators should consult the Instructions for Completing the Application found on pages 29–32. Please note that the minimum required font size for the Project Plan is **11 point with 1-inch margins**. Please check our website for updates.

Applicants should submit 12 copies of each application to the address listed above. At least one of these should be unbound; we also request a CD of all application materials.

Deadline for Applications: Applications for RFA 10-1 must either reach the offices of the Health Effects Institute by **MAY 6, 2010, or be sent by overnight air delivery service postmarked by that date**. Applications not meeting these conditions will not be considered.

Applications should be submitted to the address listed below. HEI will acknowledge receipt of the application.

Ms. Sarah Rakow
Health Effects Institute
101 Federal St, Suite 500
Boston, MA 02110

RFA 10-1: EVALUATION PROCESS

Applications will be evaluated by HEI in a two-stage process: an external review followed by an internal review by HEI's Research Committee.

EXTERNAL REVIEW

Applications will undergo a competitive evaluation of their scientific merit by and *ad hoc* panel of scientists selected for their relevant expertise in the areas of the proposed research. The panel will evaluate applications according to the following criteria:

- Scientific merit of the research design, approaches, methodology, analytical methods, and statistical procedures;
- Relevance of the proposed research to the objectives of the RFA;
- Personnel and facilities, including:
    - Experience and competence of the principal investigator and multidisciplinary team and evidence that they are all involved in the planning and conduct of the study;
    - Adequacy of effort on the project by scientific and technical staff
    - Adequacy of facility
    - Reasonableness of proposed cost

INTERNAL REVIEW

The internal review is conducted by the HEI Research Committee and generally focuses on the applications ranked highly by the review panel. In its evaluation the Committee considers the comments and recommendations of the external reviewers. The Research Committee review is intended to ensure that the studies funded constitute a coherent program addressing the objectives of the RFA. The Research Committee makes final 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 experimental techniques and a rationale for the proposed study indicating its importance in light of current insights and knowledge about vehicle emissions. It should also provide justification for the follow-on study in light of the main findings of the initial study. It is essential that both the scientific questions being addressed and the methodological approach be explained clearly. When critical, the experience of the investigators and the availability of any special equipment and facilities should be mentioned. The preliminary application must be no more than five pages in length (references are not included in the 5-page limit). No forms are necessary. 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 29) 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
Health Effects Institute
101 Federal St, Suite 500
Boston, MA 02110, USA
Tel: 617-488-2345; Fax: 617-488-2335

Eight copies of the full application for a follow-on study are needed by HEI for the review process. At least one of these should be unbound; we also request a CD of all application materials. 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 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, site visits, 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.

HEI PROJECT NEGOTIATION, MANAGEMENT, AND INVESTIGATOR COMMITMENTS

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 Department of Health and Human Services (DHHS) concerning protection of human subjects (see pages 25–26). This is 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 A.

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 (page 21).

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 sometimes conducts 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 B.

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, a summary of its independent review of the study. 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 industry and EPA sponsors, the scientific community, libraries that serve medical and scientific communities, and the general public. In addition, the HEI research reports are registered with the National Technical Information Services. Reports that have been published are indicated in Appendix C and are available on HEI's website, *www.healtheffects.org*.

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. The publication policy specific to the results derived from studies funded under RFA 10-1 is discussed on page 13 of the RFA. 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 29). 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, analysis, and justification to assure HEI that the proposed costs are reasonable for every budget category and that adequate accounting procedures will be used. HEI has no specific limitation on the budgets of research proposals. The budget should be prepared assuming a project start date of March 1, 2011. HEI expects to fund up to three studies for each phase of this RFA, with an anticipated total funding of up to $5 million (including indirect costs).

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 page 25-26).

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.

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.

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).

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.

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 and provide sufficient information in the Project Plan and in any appendix to facilitate an effective review. Applicants are encouraged to be specific and informative and avoid redundancies. Sections A, B, and C together should total no more than 6 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. There is no limit on page number for Section D. **All sections should use a minimum 11-point font size or larger and 1-inch margins**.

A. Objectives and Information About the Research Team

State concisely and realistically what the research described in this application is intended to accomplish and/or what hypothesis is to be tested. **This section should include also the information listed on page 6 of the RFA on the team qualification and general plan for the study (see page 13). Application missing this information will not be considered.**

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 the RFA 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 (including exposure generation and/or characterization) so that it can be understood clearly by the reviewers. Applicants should provide details of exposure generation 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 20). 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 FACE PAGE 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 A*). 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 19-20. 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 A 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. **Do not attach copies of the personal data form to the duplicated copies of this 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/funding.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*)

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

APPENDIX A: 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 B: 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.

APPENDIX C: HEI STUDIES AND RESEARCH REPORTS FROM 1998–2009

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)

RFA 08-1: RELATIONSHIP OF INDOOR, OUTDOOR AND PERSONAL AIR (RIOPA): FURTHER ANALYSES OF THE RIOPA STUDY DATA
Studies under negotiation

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. (2009)

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. (2009)

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. (2010)
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
Studies under negotiation

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. (2010)

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. (Completed)
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. (2010)

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. (2010)

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. (2012)
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. (2010)
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. (2009)
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. (Completed)
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. (2010)
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. (2010)
Jennifer Peel, Colorado State University
Impact of improved air quality during 1996 Atlanta Olympic Games on multiple cardiorespiratory outcomes. (Completed)
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. (2010)

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)

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. (Completed)

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. (Completed)
Zhengmin Qian, Penn State University
Association of daily mortality with ambient particle air pollution and effect modification by extremely hot weather in Wuhan, China. (Completed)
Nuntavarn Vichit-Vadakan, Thammasat University
Estimating the mortality effects of air pollution in Bangkok, Thailand. (Completed)
Chit-Ming Wong, University of Hong Kong

Interaction between air pollution and respiratory viruses: time-series studies for daily mortality and hospital admissions. (Completed)
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. (Completed)

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. (Completed)

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. (2009)
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. (Completed)
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. (Completed)

RFA 00-1: EFFECTS OF DIESEL EXHAUST AND OTHER PARTICLES ON THE EXACERBATION OF ASTHMA AND OTHER ALLERGIC DISEASES
Richard Effros (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 st
udy: 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)

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