Request for Applications

HEALTH EFFECTS INSTITUTE

January 2009

Winter 2009 Research Agenda

RFA 09-1 Methods to Investigate the Effects of Multiple Air Pollution Constituents

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 2009 RESEARCH AGENDA

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INTRODUCTION

This booklet contains the Winter 2009 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 09-1: METHODS TO INVESTIGATE THE EFFECTS OF MULTIPLE AIR POLLUTION CONSTITUENTS

Request for Applications 09-1, on pages 5–11 seeks proposals for the development of innovative statistical methods for the characterization of air pollutant mixtures and/or the study of the health effects of air pollution mixtures. As much as $750,000 will be available for studies funded under RFA 09-1. HEI expects to fund up to 3 studies, of up to roughly 2 years' duration, at $100,000 to $150,000 per year.

Letters of Intent for RFA 09-1 are due on February 16, 2009; applications are due on March 31, 2009. Twenty printed copies and one electronic copy of each application are needed for HEI's review process.

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 15-18.

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 page 17.

THE HEI RESEARCH PROGRAM

The HEI research program has addressed many important questions about the health effects of a variety of pollutants, including carbon monoxide, methanol, diesel exhaust, several air toxics (aldehydes, benzene, 1,3-butadiene), nitrogen oxides, ozone, oxygenates added to fuel, and ambient particulate matter. 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, animal, controlled human exposure, and epidemiologic studies. The choices of which pollutants to study or scientific questions to investigate have been made based on many considerations, including evaluation of issues raised by HEI's sponsors and analysis of the regulatory needs and uncertainties about health effects of specific pollutants. 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 2005, after extensive consultation with sponsors, scientists, and other constituents, HEI issued a new five-year plan, the *HEI Strategic Plan for Understanding Health Effects of Air Pollution 2005–2010*, which describes research and review priorities and plans for implementing them. Recognizing that quality science requires seeking out and validating new methods to design more informative studies, the plan highlights innovation and validation as a theme. For example, the plan emphasizes the importance of using new technologies—such as genomics and proteomics—in identifying health effects endpoints provided such endpoints provide meaningful information about the effects of air pollution.

The 2005–2010 Plan describes four priority topics :

- **Health Effects of the Air Pollution Mixture**, including developing a major research program to systematically evaluate the relative toxicity of different PM components and gaseous pollutants and research to improve our understanding of exposure to and health effects of air toxics, with a focus on areas likely to have high levels of exposure.
- **Emerging Technologies and Fuels**, including the Advanced Collaborative Emissions Study, a collaborative effort that involves chemical and physical characterization and health effects testing of emissions from diesel engine/control technology systems designed to meet stringent emission standards for PM and nitrogen oxides (NOx) that went into effect in 2007 and will be further tightened in 2010.
- **Assessing the Public Health Impact of Air Quality Actions (Accountability)**: building a larger and broader accountability research program to assess the health effects of actions taken to improve air quality.
- **Enhanced International Perspective**: continuing international contributions to HEI's US-focused scientific efforts as well as continuing the work in Asia and in other parts of the world (*e.g.,* Latin America).

For more detailed information, please see Appendix A, which provides sections from HEI's current strategic plan on research priorities and plans for implementing them. The entire plan is available on HEI's website, *www.healtheffects.org*.

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 perhaps a more challenging area of scientific investigation than is often realized by industry, policymakers, or the general scientific community. HEI seeks to develop a community of scientists and scholars who can generate new collaborations and fresh approaches to the problems of air pollution. To this end, HEI has funded both established and early-career investigators, attracting a number of scientists into this area who did not work in it before.

RFA 09-1: METHODS TO INVESTIGATE THE EFFECTS OF MULTIPLE AIR POLLUTION CONSTITUENTS

INTRODUCTION

Polluted air is a complex mixture of gaseous, liquid, and solid components, which varies greatly in composition and concentration across the United States and around the world owing to differences in sources, weather, and topography. Air pollution also varies from day to day and by season within a region. Although it is clear that people are exposed to complex mixtures of pollutants emitted by diverse sources, the U.S. Clean Air Act and most existing air quality guidelines and standards focus on the control of a common set of pollutants, called "criteria pollutants." Given this regulatory approach, it is perhaps not surprising that the vast majority of data on ambient air pollution levels and on human exposures and their health effects has also focused on these individual constituents.

Health effects research has focused largely on quantifying the marginal effects of individual pollutants, but attributing health effects to exposure to individual pollutants within complex mixtures is extremely challenging, particularly when levels of pollutants are highly correlated. As a result, fitting multi-pollutant models using conventional regression approaches frequently produces results that are difficult to interpret. This has led to the use of risk estimates for individual, often correlated, pollutants derived from the same study in separate health risk assessments for each of those pollutants.

At the same time, scientists and regulators have long acknowledged the need to go beyond this framework to understand better the effect of exposure to the mixtures of air pollution that people actually breathe. The extent to which broad mixtures of ambient pollutants play a role in contributing to or modifying the observed associations between single pollutants and a range of health outcomes is an important issue that is raised repeatedly in the policy arena, for example in the report of the *National Research Council Committee on Air Quality Management in the United States* (NRC, 2004) which called for moving the entire air quality management system to a multi-pollutant approach.

Of particular interest is the extent to which the co-mixture of pollutants in ambient air plays a role in contributing to or modifying the observed associations between individual pollutants and a range of health outcomes. Multiple pollutants together may elicit biologic or health effects that are synergistic, additive, or less than additive. Advancing scientific understanding will require improved statistical methods to investigate the joint effects of air pollution constituents — in other words, to determine how the effects of a mixture as a whole differ from the effects of individual pollutants within the mixture.

HEI is interested in funding studies that develop statistical methods to further the understanding of how pollutants occur together and/or the potential influence of the combination on the health effects relative to the effects attributed to the individual pollutants within the mixture. Exploring the health effects of the air pollution mixture is one of the four priority areas identified in HEI's *Strategic Plan 2005–2010* (see Appendix A). In addition, it is directly in line with HEI's commitment to innovation and validation, particularly to continually improving and validating state-of-the-art statistical techniques for epidemiologic analysis.

RFA 09-1 seeks to support the development of innovative statistical methods for the characterization of air pollutant mixtures and/or the study of the health effects of air pollution mixtures. Methods investigating the joint effects of air pollution constituents (i.e., exploring how the effects of a mixture as a whole differ from the individual or combined effects of individual pollutants within the mixture) are relevant. Also relevant are proposed methods for the quantification of exposure to multiple air pollutants, along with the impact of exposure measurement error on observed inter-pollutant correlations. Methods may include either innovative research designs or analytic techniques and may apply to observational or experimental studies in human populations or animal models. Novel adaptation and application of statistical methods from other fields are strongly encouraged.

As much as $750,000 will be available for studies funded under RFA 09-1. HEI expects to fund up to 3 studies, of up to roughly 2 years' duration, at $100,000 to $150,000 per year.

BACKGROUND

There is now a clear recognition that statistical methods are needed to ascertain whether effects associated with a given mixture (1) can be detected separately from the effects of the chemical constituents of the mixture (combined effects of individual pollutants within complex pollutant mixtures) or (2) can serve as a marker for the particular mixture in which it is found (effects of a pollutant mixture).

COMBINED EFFECTS OF INDIVIDUAL POLLUTANTS WITHIN COMPLEX POLLUTANT MIXTURES

1 HEALTH EFFECTS CONTEXT: Most epidemiologic studies have focused on the effects of individual pollutants, when a large part of the effects may actually be attributable to the combined effects of multiple pollutants. Thus, there needs to be a shift in emphasis from single-pollutant models to multipollutant models addressing the combined effects of pollutants, so that the effect of a spectrum of pollutants can be better ascertained. Since the composition of mixtures varies in space and in time, spatial and temporal variability could be exploited when an attempt is made to disentangle the marginal effects of individual pollutants within the mixture. The challenges of determining the additive effects, effect modification, synergy, and less-than-additive effects in epidemiologic studies are substantial (Mauderly & Samet 2008), however. Measurement error contributes additional complications; pollutants that are better measured will tend to dominate the estimation, even if their effects are less strong.

2 STATISTICAL CONTEXT: When data sets contain measurements of many constituents of air pollution obtained at different places and time points together with health outcomes, and when there is sufficient variability in these data, multivariate analyses of the association between constituents of air pollution and health outcomes may be possible. Such analyses are aimed primarily at estimating the effects of specific constituents of interest, while accounting for so-called independent effects. Moreover, multivariate regression models can be used to detect departures from additivity. It is well recognized that simply introducing a number of co-pollutants (and associated product terms) simultaneously into a regression analysis and carrying out multivariate rather than univariate regressions has its limitations. Indeed, high degrees of correlation between covariates render the results statistically unstable and difficult to interpret, and stepwise methods are inadequate in the presence of strong collinearity. In line with recent developments in applied statistics, a number of advanced statistical methods might be envisaged, ranging from (but not restricted to) shrinkage methods and penalized regressions, hierarchical modeling with clustering of "similar" regression coefficients, stochastic variable selection that explores large model spaces, and methods specifically aimed at finding combinations of exposures.

Determining which methods are appropriate to the specific context of research on air pollution and health, proposing new statistical approaches, and comparing and demonstrating their use are important and difficult topics, for which research is encouraged. Whatever method is chosen to deal with multi-collinearity, sensitivity of the results to different structural choices and to method-specific tuning constants is expected. Thus, it will be important to design sensitivity studies and/or simulation studies that shed light on these choices. Moreover, co-pollutants often have a wide range of degrees of variability and measurement error, as well as different patterns of inter-pollutant correlation. Hence, quantitative methods that take into account the potential influence of measurement errors within the chosen statistical framework are needed.

CHARACTERIZATION OF THE EFFECTS OF A POLLUTANT MIXTURE

1 HEALTH EFFECTS CONTEXT: The relative importance of individual pollutants within a mixture is dependent on local, regional, temporal, and meteorologic differences. Local or regional differences in the relative proportions of pollutants within a mixture, including differences between downtown urban and rural areas, as well as global regional differences in inter-pollutant correlations must be better characterized. Temporal differences (daily, seasonal, demand-driven, and/or scheduled changes in emissions of sources) also affect the relative components within the mixture. Meteorologic conditions (e.g., the summertime effects on ozone concentration or winter inversion effects on pollutant levels) can have a substantial impact.

To date, methods to address how pollutants act as a mixture over time and space have been hampered by strong correlations between pollutants in given mixtures. Source apportionment methods attempt to address this problem by classification of "mixtures"-specific sources through the use of source-specific markers. These approaches then attempt to use orthogonal source mixtures in a given environment to evaluate their individual or combined contributions to health effects. However, these techniques are not capable of addressing the larger, combined mixture effects of all of the sources. They are frequently not based, either, on a solid understanding of the underlying biological plausibility of any one source mixture's relation to health. In addition, the influence of errors in the measurement of individual pollutants within the mixture will have to be carefully considered, as well

as the temporal structure and other concomitant factors that may influence the source attribution.

2 STATISTICAL CONTEXT: The term *latent-variable methods* is usually applied to models in which there are multiple variables but at least one variable is unobserved (or latent). Factor-analysis is a special type of latent-variable model in which it is assumed that multiple variables are linked through their association with a small number of latent variables, called factors. It is recognized that the decomposition required when applying such models is subject to non-identifiability and sensitivity to assumptions. The clarification of statistical and computational hypotheses underlying commonly used latent-variable models and the comparison of current practice with other latent factor models are important. For example, at present, source-apportionment models and multivariate receptor models are used as "black box tools" and are not sufficiently linked to mainstream statistical practice. An additional concern is that the inherent variability of the current source apportionment is not reflected in the estimation of the association with the health outcomes, thus rendering reproducibility and the comparison between different studies difficult. Alternative modeling approaches that facilitate a better understanding of the variability within mixtures, as well as the conditions under which a robust interpretation of the characterization of these mixtures can be made, would be welcome.

OBJECTIVES OF THE RFA

OBJECTIVES

The overall objective of RFA 09-1 is to fund the development of **innovative statistical methods for the characterization of air pollutant mixtures and/or the study of the health effects of air pollution mixtures**. Methods investigating the joint effects of air pollution constituents (i.e., exploring how the effects of a mixture as a whole differ from the effects of individual pollutants within the mixture) are welcome. Also welcome are proposed methods addressing the quantification of exposure to multiple air pollutants, along with the impact of exposure measurement error on observed inter-pollutant correlations.

- Innovative methods may include either research designs or analytic techniques and may apply to observational or experimental studies in human populations or animal models.
- Novel adaptation and application of statistical methods from other fields (i.e., cross-fertilization) is strongly encouraged.

SPECIFIC OBJECTIVES

1 RFA 09-1 seeks to support the development of innovative statistical methods for the study of the combined effects of individual pollutants within complex pollutant mixtures. Analytic approaches may include improvement of multivariate methods and development of strategies for their application or the proposal of new approaches. Of particular interest are multivariate methods adapted to the study of highly correlated pollutants, and methods to detect the presence of interactions between two or more pollutants and to evaluate their combined effects. All methods proposed must include validation of the approach using either simulation studies or a thorough sensitivity analysis on widely available data sets.

2 RFA 09-1 seeks to support the development of innovative statistical methods for the study of health effects of air pollution mixtures in animal models and human populations. Of particular interest are methods for characterizing mixtures emitted by specific sources or groups of sources.

DATA

Applications of proposed methods to existing or pilot data are strongly encouraged. Major original data collection is beyond the scope of RFA 09-1. Methods need to be motivated by and illustrated by application to real-life data. While simulations may be used to demonstrate performance, proposals relying exclusively on simulated data will not be considered responsive.

POSSIBLE SOURCES OF DATA

1 Relationships of Indoor, Outdoor, and Personal Air (RIOPA) Database: Funded by HEI and prepared and maintained by Atmospheric and Environmental Research, Inc. (AER), this database contains information collected in the RIOPA study (Weisel et al. 2005; Turpin et al. 2007) that was co funded by HEI and the National Urban Air Toxics Research Center (NUATRC) and conducted in three cities with different air pollution source profiles: Los Angeles, California; Houston, Texas; and Elizabeth, New Jersey. *http://riopa.aer.com*

2 HEI Air Quality Database: Prepared and maintained by AER, this database focuses on the levels of $PM_{2.5}$ components and gaseous pollutants at and near sites in the EPA's $PM_{2.5}$ Chemical Speciation Trends Network

(STN) and State, Local and Tribal Air Monitoring Stations (SLAMS). Currently, the database contains information on speciated PM components and gaseous pollutants at these sites for the years 2000 through 2006. *http://hei.aer.com*

3 Internet-Based Health and Air Pollution Surveillance System (iHAPSS): Funded by HEI and developed and maintained by the Department of Biostatistics at the Johns Hopkins Bloomberg School of Public Health, iHAPSS contains data and analytic software from the National Morbidity, Mortality and Air Pollution Study (NMMAPS). *http://www.ihapss.jhsph.edu/*

4 Air Quality System (AQS) Data Mart: The AQS Data Mart contains every measured, daily aggregate and annual aggregate value collected and calculated by the U.S. Environmental Protection Agency (EPA) since January 1, 1980. Designed to make air quality data more accessible and useful to the scientific and technical community, the database includes raw and summary (daily and annual) pollutant values, descriptive and administrative descriptions for monitors, sampling methods and schedules, as well as analytic methods used. *http://www.epa.gov/ttn/airs/aqsdatamart/*

HEI also welcomes studies developing better statistical approaches for these questions for use in toxicological studies. Although there are no comparable large publicly available toxicological data bases available, we would encourage interested investigators to contact the National Environmental Respiratory Center (NERC), where researchers are currently compiling results from laboratory studies of common source emissions to develop a composition-concentration-health response database to evaluate the contribution of individual contaminants, including diesel, wood smoke, and gasoline emission, to the health effects observed in air pollution mixtures (http://www.nercenter.org).

We intend to bring funded investigators together to discuss proposed methods and to identify a publicly available, common set of data on which to validate all methods developed. The use of publicly available data sets is strongly encouraged; at the very least, data sets should be made available to other analysts interested in testing and comparing related methods.

SOFTWARE REQUIREMENTS

All software and programs proposed must be widely available with reproducible results, so that any methods developed can be readily applied elsewhere. Open source software (e.g., R) is preferred.

REFERENCES

Mauderly JL, Samet JM. 2008. Commentary: Is there evidence for synergy among air pollutants in causing health effects? Environ Health Perspect 117:1–6.

NRC (National Research Council), Committee on Air Quality Management in the United States. 2004. Air Quality Management in the United States. National Academies Press, Washington, DC.

Turpin BJ, Weisel CP, Morandi M, Colome S, Stock T, Eisenreich S, Buckley B, and Others. 2007. Relationships of Indoor, Outdoor, and Personal Air (RIOPA). Part II: Analyses of concentrations of particulate matter species. Research Report 130. Health Effects Institute, Boston, MA.

Weisel CP, Zhang J, Turpin B, Morandi MT, Colome S, Stock TH, Spektor DM, and Others. 2005. Relationships of Indoor, Outdoor, and Personal Air (RIOPA). Part I: Collection methods and descriptive analyses. Research Report 130. Health Effects Institute, Boston, MA.

RFA 09-1: APPLICATION PROCESS AND DEADLINES

LETTER OF INTENT

Although not required as part of the application process, Letters of Intent are requested by HEI because they provide information on the likely response to the RFA and help HEI staff to organize the application review process. Applicants are encouraged to submit a Letter of Intent (maximum of 3 pages, single spaced) summarizing the proposed project before submitting an application. The Letter of Intent should specify the research goals of the project and indicate the general approach to be used. HEI may contact the applicants to advise them how to make their applications more responsive to the specific objectives of the RFA.

Deadline for Letter of Intent: The Letter of Intent should be received no later than **FEBRUARY 16, 2009,** by mail, fax, or e-mail at the following address:

Ms Terésa Fasulo
Science Administration Manager
Health Effects Institute
101 Federal St, Suite 500
Boston, MA 02110-1817, USA
Tel: +1-617-488-2345
Fax: +1-617-488-2335
tfasulo@healtheffects.org

FULL APPLICATION

Full applications must be submitted on the forms **F-1 to F-10** (see list on page 23) that can be found on our website at *www.healtheffects.org/funding.htm*. Investigators should consult the Instructions for Completing the Application found on pages 19–22. The required font size is **11 point.** Please check our website for updates. **Applicants should submit 20 copies of each application** to Ms. Terésa Fasulo at HEI at the address above. At least one of these should be unbound; we also request a CD of all application materials.

Inquiries regarding the application and evaluation procedures should be directed to:

Dr Sumi Mehta at +1-617-488-2306
smehta@healtheffects.org or

Dr Rashid Shaikh at +1-617-488-2301
rshaikh@healtheffects.org

Deadline for Applications: Applications for RFA 09-1 must either reach the Health Effects Institute by **MARCH 31, 2009, or be sent by overnight air delivery service postmarked by that date.** Applications not meeting these conditions will not be considered. HEI will acknowledge receipt of the application.

RFA 09-1: EVALUATION PROCESS

HEI is committed to facilitating research on the health effects of air pollutants from automotive emissions and other sources by encouraging applications from researchers with skills and methods in various disciplines, including those not conventionally associated with this field. Procedures and criteria for evaluation of applications have been designed with these goals in mind.

Applications received will be evaluated by HEI in a two-stage process: an external review followed by an internal review.

EXTERNAL REVIEW

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

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

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

INTERNAL REVIEW

The internal review is conducted by the HEI Research Committee and generally focuses on the applications ranked highly by the external review panel. The review is intended to ensure that the studies funded constitute a coherent program addressing the objectives of the Institute. The Research Committee makes recommendations regarding funding of studies to the Institute's Board of Directors, which makes the final decision.

POLICY ON FOLLOW-ON APPLICATIONS

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

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

PROCESS AND TIMING FOR SUBMISSION

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

PRELIMINARY APPLICATION

The preliminary application should contain two elements: a description of the project plan containing an outline of the intended 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) curriculum 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 23) 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. Terésa Fasulo
Science Administration Manager
Health Effects Institute
101 Federal Street, Suite 500
Boston, MA 02110, USA

Tel: +1-617 488-2345
Fax: +1-617 488-2335
tfasulo@healtheffects.org

Fifteen 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 PROJECT NEGOTIATION, MANAGEMENT, AND INVESTIGATOR COMMITMENTS

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

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

SCIENTIFIC NEGOTIATION OF PROJECT PLANS

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

RESEARCH AGREEMENT (CONTRACT)

Upon satisfactory negotiation of the project plan and budget, a contract for the study is negotiated with the Principal Investigator's institution. HEI's Research Agreement is a cost-reimbursement contract rather than a grant. Investigators should be aware that because scientific and administrative contract negotiations may extend through a period of several months, and may result in changes in the scope or cost of the proposed study, certain portions of the applications may have to be updated prior to contract signing. In general, HEI requires that any significant changes in personnel, scope of work, and/or budget be reflected via submission of revised budgets, project plans, or other appropriate application materials prior to the signing of the contract. For human studies and major animal studies, a protocol and Standard Operating Procedures (SOPs) should be written before the study starts (see *Use of Human Subjects and Quality Assurance Program* below).

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

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

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

STUDIES INVOLVING HUMAN SUBJECTS

As mentioned in the section *Instructions for Completing the Application, Additional Submissions*, the applicant must submit, with the application, a written assurance for compliance with the guidelines established by the Department of Health and Human Services (DHHS) concerning protection of human subjects (see pages 21–22). 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 C.

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

A qualified individual selected by HEI will serve as a quality assurance officer to aid in HEI's assessment of QA activities in a study. The QA officer may conduct periodic audits to ascertain compliance with the study protocol or to examine records. He or she reports to HEI's Director of Science. The audit reports are confidential and are not released to persons not directly involved in management of the project.

PROGRESS REPORTS

Progress reports are one of the ways by which HEI keeps informed of the progress of the studies that it supports. Investigators are required to submit progress reports at five and ten months of the first year of the study. In subsequent years, generally five- and ten-month reports are requested as well. In certain cases HEI science staff may indicate that submission of a 5-month report is not necessary. In the final year of the contract, the ten-month progress report is replaced by a comprehensive final report (page 17).

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 D.

FINAL REPORT

HEI has set as one of its goals to publish research reports of the highest scientific quality that will be of value to regulators, government officials, scientists, and the interested public. After a study is completed, each HEI-funded Principal Investigator prepares a comprehensive final report that describes the study and its findings. Because some of HEI's research projects are designed to provide information to be used in regulatory decisions, HEI places an emphasis on timeliness.

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

Each draft final report is peer-reviewed by scientists with appropriate technical expertise, including a biostatistician. A compilation of the comments of the reviewers, together with the Review Committee's initial review, is sent to the investigator, who has an opportunity to respond to these comments and, if necessary, to revise the report. Occasionally, the Review Committee may request major changes such as additional analyses. Subsequently, the Review Committee prepares its commentary. The investigator is given an opportunity to comment on the commentary prior to publication. The contractual obligation to prepare a comprehensive final report and to participate in the HEI review process distinguishes HEI from most other funding agencies. Potential applicants should be aware of the effort associated with this responsibility.

The HEI Research Reports, which consist of the investigator's final report and the Review Committee's commentary, are the principal means by which the Institute communicates results of its research and review processes. They are distributed to the motor vehicle industry, the EPA, the scientific community, libraries that serve medical and scientific communities, and the general public. In addition, the HEI research reports are registered with the National Technical Information Services. Reports that have been published are indicated in Appendix B and are available on HEI's website, *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. 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 23). Applications should be typed single-spaced, within the margin limitations indicated on the forms. Interactive forms can be downloaded from our website at *www.healtheffects.org/ funding.htm*.

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

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

BUDGET

Cost or Pricing Data: Provide adequate data and analysis to assure HEI that the proposed costs are reasonable and that adequate accounting procedures will be used. HEI has no specific limitation on the budgets of research proposals. Most of those funded to date have been within a range of $70,000 to $300,000 per year, including indirect costs. Projects requiring larger budgets or time periods longer than three years must have exceptional promise of developing important methods or information for understanding the health effects of automotive emissions. For applications responding to RFA 09-1, the budget should be prepared assuming a project start date of September 1, 2009.

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 $750/8-hr day. HEI's participation in consultant costs is subject to limits set by federal regulations. (See also *Additional Submissions* on pages 21-22).

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

A. Objectives

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

B. Anticipated Results and Significance

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

C. Related Previous Studies

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

D. Experimental Plan and Methods

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

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

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

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

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

Include a description of the statistical methods to be used for analysis and interpretation of the data. Describe the proposed statistical procedures with sufficient detail to allow evaluation by a biostatistical reviewer.

Where appropriate, describe the procedures to be used to ensure that the quality of the data is adequate in view of the objectives of the study (see Quality Assurance on page 16). 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 C*). Approval of the study by the Institutional Review Board (IRB) at the investigator's institution is required before starting a study with human subjects. In addition, HEI will need to obtain approval from EPA before subject recruitment starts, as described under *HEI Project Negotiation, Project Management, and Investigator Commitment* on page 15. Documentation submitted to HEI should include (1) the complete application to the IRB; (2) consent forms, if applicable; and (3) a signed letter from the IRB indicating that the study has been approved or exempted.

Laboratory Animals The applicant shall provide with the application written assurance that any use of laboratory animals will comply with the provisions of the Animal Welfare Act (7 U.S.C. S 2131 et. seq.) and the guidelines set forth in the Guide for the Care and Use of Laboratory Animals. These documents are available from the Office for the Protection from Research Risks, National Institutes of Health, Bethesda, MD 20892. If laboratory animals are to be used in the proposed studies, state the species, strains, ages, and numbers of the animals involved and the methods to be used to comply with the above-mentioned guidelines.

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

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

Consultants Consultant arrangements must be confirmed in writing. Attach appropriate letters from each individual, confirming his or her role in the project.

Quality Assurance It is HEI's policy to apply its special QA procedures to all approved research projects that are anticipated to produce data of regulatory significance. This includes all human studies, as well as certain designated animal studies. See Appendix C for more details.

Personal Data HEI has a continuing commitment to monitoring the operation of its review and award process to detect, and deal appropriately with, real or imagined inequities with respect to age, ethnicity, race, or gender of the proposed principal investigator. To provide HEI with the information needed to fulfill this commitment, we request that each applicant complete the optional personal data form (Form F-10) and attach it as the last page of the signed original application. **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 PDF and RTF format.

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: SECTIONS OF THE HEI STRATEGIC PLAN (2005–2010)

HEI's strategic plan describes the projected research program and scientific review activities for the period 2005–2010. This plan was developed with ideas and input from HEI's sponsors, the scientific community, and other constituents. To provide information to applicants about HEI's mission, views about important research needs, and research priorities, several sections of the current strategic plan are included in this Appendix. The entire plan can be found on HEI's website, *www.healtheffects.org*.

These activities largely mirror and take the logical next steps on the key initiatives of HEI's 2000–2005 plan. In addition, at the urging of our sponsors and others, HEI will infuse innovation and validation throughout its program to bring into the mainstream of health risk research the latest emerging molecular biology techniques (*e.g.,* genomics, proteomics) and to continuously identify, validate, and improve state-of-the-art statistical techniques for epidemiology.

MAJOR RESEARCH OPPORTUNITIES 2005–2010

Several substantial projects and research programs currently under way are being continued in the Strategic Plan 2005–2010. HEI will focus these initiatives on the topics to which we can best contribute and on bringing HEI's capabilities in *innovation* and *validation* into every aspect of our work.

INNOVATION AND VALIDATION

HEI's mission is to provide high-quality science that is reviewed, interpreted, and communicated thoughtfully and completely so that the best information is available for regulatory and other decision-making. An important aspect of quality science is to seek out new methods, both experimental and statistical, to design better, more informative studies. Several examples of ways in which HEI's work can be enhanced by using new methods and improving and validating current methods are summarized below.

Innovative Techniques

HEI has sought to develop a community of scientists who can generate new collaborations and fresh approaches to air pollution problems, to attract scientists from other fields who could bring innovative methods to the study of air pollution, and then to subject those approaches to rigorous analysis and review to ensure they are applied thoughtfully. Under this strategic plan, we will increase our efforts to incorporate new methods and types of health endpoints. One important example is identifying and applying new genomic, proteomic, and other methods in ways that will provide meaningful information about susceptibility to effects of air pollutants and about changes relevant to health effects induced by air pollutants. We will also strengthen our efforts to encourage investigators to collaborate with scientists in other fields so that new methods appropriate to the questions of interest can be brought more quickly and successfully into HEI studies.

Improvement in Epidemiology Methods

In May 2003, HEI issued a Special Report on revised analyses of nearly 30 time-series epidemiologic studies along with Commentaries from a Special Review Panel. Investigators conducted revised and alternative analyses after HEI and other investigators identified important questions about the statistical package that has been used widely for time-series analyses of air pollution and health. In their Commentaries, the Panel raised questions about possible continuing confounding of time-series results by factors (such as weather) that may covary in time with air pollutants. In the APHENA study, investigators from North America and Europe are addressing these questions by testing different statistical approaches and applying them across 120 US, Canadian, and European cities. A new Special Panel will rigorously review these new methods and will prepare a Commentary on how well the investigators have addressed confounding. HEI will oversee closely any future time-series studies, as well as other types of epidemiologic studies, to ensure that they adhere to the latest, most effective ways to control for time-covarying factors and address any remaining issues.

Increased Access to Research Data

HEI has always required that investigators report all of their results and has always made data from HEI studies available. In the coming years, HEI will be able to provide not only results but also access to databases and software packages on the Web. In response to widespread interest in the data and methods used in the NMMAPS

project and growing calls and requirements for data access, HEI funded the Internet Health and Air Pollution Surveillance System (IHAPSS) at the Johns Hopkins Bloomberg School of Public Health to build a fully Web-accessible database of all NMMAPS air pollution, health, and weather data and all programs used to analyze these data. HEI and the NMMAPS investigators brought together a user group of scientists, government officials, industry, and others to evaluate the website, to consider the value of maintaining and updating its offerings, and to advise its future directions. For other studies of high regulatory relevance that draw as broad interest as NMMAPS did, HEI will consider funding similar website development.

PRIORITY RESEARCH AND REVIEW TOPICS

Health Effects of Air Pollution Mixture

Polluted air is a complex mixture of gaseous, liquid, and solid components that varies greatly in composition and concentration across the US and around the world owing to differences in sources, weather, and topography. It also varies from day to day and by season within a region. Most air quality standards regulate specific compounds (except PM standards, which regulate a mixture). Because of the regulatory focus on specific compounds or groups of compounds, research has also tended to focus on single pollutants. However, different pollutants can cause similar responses, often through different mechanisms. Two or more pollutants together may elicit biological or health effects that are additive, more than additive, or less than additive. Current knowledge about these interactions is taken into account in setting the NAAQS, but a more comprehensive understanding is needed.

Despite a great deal of interest over several decades in understanding more about assessing toxicity of mixtures and how to regulate them, little progress has been made beyond understanding interactions among small numbers of pollutants. HEI has identified two steps toward a better understanding:

- Undertake targeted research programs on PM and gases and on air toxics, two important mixtures within the broader air pollution mixture.
- Convene a workshop and an expert working group to examine and evaluate innovative approaches to conducting research on and regulating health effects of mixtures and to write a monograph on this topic.

PM and Gases A major element of HEI's research over the past decade has been investigating health effects of PM and gaseous pollutants. We expect in the near term to complete the review and publication of a number of ongoing studies, to continue to address recently identified methodologic issues in time-series epidemiology studies, and to increase access to PM research and data. Most importantly, for 2005–2010 HEI has launched planning initiatives for a systematic approach to assessing the relative toxicity of characteristics and sources of PM along with other parts of the ambient air pollution mixture.

Completing, Reviewing, and Communicating Results of HEI Studies In the near term HEI is continuing its work on PM with 23 studies under way and 6 reports under review. These PM studies cover several major topics: dose and exposure assessment, effects of diesel and other PM on allergic responses, initial efforts to measure toxicity of PM components and sources, mechanisms of health effects, and epidemiologic studies of short- and long-term effects in North America, Europe, and Asia.

Assessing Toxicity of PM Components, Gases, and Sources Building on HEI and other research on mechanisms of PM health effects and PM components related to toxicity (HEI Perspectives, April 2002), HEI has been developing plans to address more systematically the toxicity of specific components and characteristics of PM (and ultimately sources of those components). Although epidemiologic evidence associates PM with health effects, the components that may cause the greatest effects remain unknown. As initial decisions to reduce overall PM levels go forward—decisions based on the premise that all fine particles are problematic—the need to better understand toxicity of PM components and gases becomes increasingly important for the long-term agenda to reduce exposure. The NRC Committee on Research Priorities for Airborne Particulate Matter (NRC 2004b) and HEI (Strategic Plan 2000–2005) have noted the importance of this area.

Over the past year, an HEI Research Committee Working Group with expertise in epidemiology, toxicology, air quality, and statistics took steps to gather and evaluate information needed to design a multisite research program on health effects of PM components. The Group had two main goals:

- **Develop a database of relevant air quality and other information.** In February 2003, in order to move rapidly to meet the health science community's need for an accessible and complete source of air quality data, HEI funded a group to develop a database that will provide information useful in designing and conducting epidemiologic and toxicologic studies of health effects of PM components in different regions. These data are

air pollution data from the EPA PM speciation network and other monitoring stations across the US (maintained by the EPA and state and local air quality agencies) that measure levels of PM and gaseous pollutants. The data are being characterized in terms of spatial and temporal variation and proximity to sources. Other information, such as how to access health and weather data, will be included in the database. A Web-accessible database will be available in mid 2005.

- **Hold a workshop to discuss information and study designs.** HEI held this workshop in August 2004. Participants presented and discussed papers on available air pollution and health data and on toxicologic and epidemiologic approaches that could be used in designing multisite studies.

The Research Committee is now deciding exactly how to frame an RFA for research on toxicity of PM components, which will be issued in mid 2005. Recognizing that any scientific advances in this complex area must be attained through collaboration across scientific disciplines, the Committee is developing plans that will enable investigators to have time to put together multidisciplinary teams involving toxicologists, epidemiologists, air quality experts, statisticians, and other experts to evaluate the feasibility of testing various hypotheses of interest and to design a sound study. The RFA is likely to allow applications for a pilot study or a full study because some scientists may be ready to design a full study and others may need time to develop a team, evaluate air quality and other information to determine what hypotheses of interest may be testable at this time, and design a study. A second RFA, expected to be issued approximately 1.5 years later, would seek additional full studies; investigators who had already conducted planning studies, as well as other scientists, could apply for these. With this dual approach, HEI hopes to get one or two major studies and several planning studies under way in the next year and then start one or two large studies the following year.

This major, multidisciplinary undertaking will involve numerous investigators and careful research design, extensive quality control and quality assurance, and innovative approaches. HEI intends to bring together diverse parties in industry, government, and the environmental community to support this effort and maximize the utility of its results.

Critical Reviews and Perspectives HEI will produce two or three new HEI Perspectives, a publication series written by the Health Review Committee for a broad audience interested in environmental health. HEI Perspectives integrate findings across several HEI studies and related research and interpret how the results bear on important and timely issues. Topics of interest are:

- **Assessment of what we have learned about cardiovascular effects of PM exposure.** Results of time-series epidemiologic studies suggesting that people with cardiovascular disease are more sensitive to PM exposure have led to toxicologic and panel studies investigating cardiovascular effects in more depth. The possible importance of the findings makes it critical to evaluate the consistency of the results across studies and the overall picture they present and to consider what future research is needed to provide more definitive results.
- **Summary and evaluation of PM exposure assessment issues,** including those related to assessing exposure in epidemiologic studies, such as the relation between central and regional site monitors and personal PM exposure, as well as relations between indoor, outdoor, and personal exposure for the general population and also for susceptible subpopulations.
- **Updated discussion of time-series and other epidemiologic studies of exposure to PM.** This discussion would integrate information from the revised analyses of NMMAPS and other time-series studies, the new methods to address time-varying confounding factors developed in APHENA, progress on long-term and other relevant studies, and suggestions for future directions.

HEI will also convene an expert panel to develop a **critical review of the literature on traffic-related health effects**, which will be published as an HEI Special Report. A number of studies have reported increased adverse health effects, such as exacerbation of asthma or allergic responses in people living near roads with high traffic or spending time in traffic. These findings have often been interpreted as effects of exposure to mobile-source emissions, but how well studies have evaluated exposure or other possible risk factors is unclear. The literature should be reviewed critically in order to interpret current findings and to make recommendations for future studies.

Air Toxics Mixture The overall goal of HEI's air toxics program has been to provide information that will reduce uncertainties in evaluating human health risks associated with exposure to mobile-source air toxics. These activities have been driven by current and future air toxics regulatory programs. These include the EPA National Air Toxics Assessment and its efforts to assess health effects of and prioritize among major air toxics, state and local efforts to assess health effects and regulate air toxics (*e.g.,* Southern California's Multiple Air Toxics Exposure Study), and source-specific regulatory programs (*e.g.,* the EPA Mobile Source Air Toxics rule).

HEI has ongoing research on mechanisms of butadiene effects and exposure to and health effects of aldehydes. We are interested in continuing to fund similar studies that could provide a greater understanding of human exposure and effects. However, our main interest in near-term future work is to increase understanding of health effects of ambient air toxics mixtures to which people are exposed.

Review of Exposure and Health Effects In addition to targeted research initiatives, in order to inform key shorter-term decisions about air toxics, an HEI expert panel is developing a concise synthesis of information about exposure to and health effects of mobile-source air toxics that will be understandable to nonscientists and useful to senior decision makers in government and industry. It will assess and summarize what we know about air toxics, as well as identify research gaps and unresolved questions. Because of the large number and diverse nature of these compounds and groups of compounds and the variability in available health effects and exposure information about them, this effort will likely focus on our understanding of effects of each of the major compounds rather than on reviewing the overall impact of exposure to the air toxics mixture (although the studies described below may eventually be able to examine these questions).

Studies of Population Exposure to Air Toxics in Potential Hot Spots Five studies are measuring a broad range of mobile-source air toxics (many of which also have other sources) in areas where air levels are expected to be high (hot spots). A variety of site types and air toxics sources are included. Specific sites include:

- the Peace Bridge border crossing area and nearby neighborhoods where trucks idle or move slowly.
- a residential area in Camden, New Jersey, close to industrial and mobile sources of air toxics.
- areas involving exposure to diesel trucks: industrial parks upwind of truck terminals; neighborhoods downwind from truck terminals; and in-vehicle exposures of truck drivers on city, suburban, and rural streets and highways.
- microenvironments dominated by mobile sources: commuter corridors, street canyons, and parking garages in the Los Angeles area.
- residential locations near heavy, moderate, and light traffic.

Many predictions of health risks from exposure to air toxics in the environment are based on modeled estimates of exposure and either potency estimates (for cancer effects) or comparison to reference concentrations (for noncancer effects). All of these measures have sizeable uncertainties related to exposure and toxic potency. Thus, information on exposure from these studies will reduce the uncertainty about health effects projections, but actual health data are also needed.

Studies in Confirmed Hot Spot Areas Follow-on health studies in some hot-spot areas, selected on the basis of exposure information, will enable comparison of health effects in areas with different combinations of air toxics and will thus provide needed information about contribution of air toxics to adverse health effects. The rationale for these studies is that people exposed in places with higher concentrations of air toxics would be expected to exhibit greater health effects. Testing whether effects are found in such locations will provide meaningful information for future risk assessment.

Emerging Technologies and Fuels

Rapid development of diesel technologies and alternative fuels, as well as longer-term technologies (such as fuel cells), aims to address concerns about air pollution, fossil fuel availability, and climate change. In light of such development, the need to evaluate future technologies is increasingly important. HEI will rely on SCET, sponsors, and others to provide input about the most important technologies and fuels over the next five years. From 2005 to 2010, we expect to conduct assessments of existing science on emission control technologies and alternative fuels. In addition, ACES will be a component of HEI's technology activities and will serve as a model for future testing of important new technologies.

Review and Assessment Projects HEI sponsors and SCET members have suggested several critical reviews of new technologies, fuels, and fuel additives that might be used in the future. Because health effects testing is expensive and time consuming, we should evaluate possible emissions and health effects at early stages of development to determine whether research on certain emissions components is needed. We expect to undertake up to two of these recommended projects (the diesel projects might be combined into one).

- **Evaluation of NO_x aftertreatment technologies for advanced diesel engines.** Possible emissions and health effects of aftertreatment technologies that will be available to reduce oxides of nitrogen (NO_x; such as selective catalytic reduction or NO_x adsorbers) should be evaluated. For example, selective catalytic reduction technology uses urea to react with NO_x to produce nitrogen and water. Questions have been raised

about the emission of new, possibly toxic nitrogen-containing compounds (such as urea decomposition products and nitroxyalkanes) and increased production of nitro-polycyclic aromatic hydrocarbons and aldehydes. To the extent that emission and health information are available, the possible health effects of these compounds could be assessed.

- **Comparison of fuels for diesel engines.** In addition to diesel fuel, and low-sulfur diesel fuel starting in 2006, alternative fuels are being considered for truck and bus fleets. Fuels of interest include compressed natural gas, Fischer-Tropsch fuel (a clean-burning liquid that can be made from natural gas, coal, and low-value refinery products), and biodiesel (which can be made from a variety of renewable sources, including animal fat and various plant oils from agricultural feedstocks or used cooking oil). These fuels are of interest because they enable taking advantage of feedstocks other than oil, may produce lower emissions of toxic pollutants from engines, and may reduce overall greenhouse gas emissions.
- **Studies of metals in fuel additives.** Some have raised concerns about persistent bioaccumulation of platinum, manganese, and other elements from mobile sources and whether these emissions are in toxic or nontoxic forms. Ferrocene, an iron-containing molecule that can be added to diesel fuel, is of possible interest depending on the likelihood of its future use. MMT, a manganese-containing compound, is being used or actively considered for use as a gasoline additive.
- **Assessment of increased use of ethanol and other alternative fuels in gasoline engines.** The US has a growing interest in phasing out methyl *tert*-butyl ether (MTBE) as a fuel additive and in substantially increasing use of ethanol as a gasoline additive (*e.g.,* through national energy legislation). Assessment of possible implications of this increase for emissions, exposure, and health, and a plan for an accountability assessment of the increase, could be timely and important.

ACES is a cooperative, multiparty effort designed to characterize emissions of new, controlled heavy-duty diesel engines being prepared for market to meet heavy-duty emission standards taking effect in 2007 (requiring reduction of PM and NO_x levels) and in 2010 (to meet even lower NO_x standards using new NO_x reduction technologies). In addition, the 2010 engines will undergo extensive health effects testing (of both chronic and key shorter-term effects) to evaluate the safety of their emissions.

HEI is responsible for study design, health study protocols, implementation, and overall reporting of results for ACES. The Coordinating Research Council is responsible for emission characterization and exposure setup. The overall effort is being guided by an ACES Steering Committee consisting of key stakeholders and funders of the effort (*e.g.,* public agencies including EPA, Department of Energy, California Air Resources Board; the private sector including the Engine Manufacturers Association, oil companies, emission control manufacturers, and others; and environmental organizations). A Health Oversight Committee, comprising several members of the HEI Research Committee and other experts, is being organized to guide planning and oversight of health effects studies in ACES. A Health Advisory Committee, made up of scientists from funding organizations and other stakeholders, will provide input. If fully funded, ACES will provide HEI with an opportunity to contribute considerably to assessing a new set of technologies before they are in widespread use.

The timeline for ACES involves detailed planning and securing of final funding by mid 2005. Assuming all necessary funding is obtained, ACES is planned to take place in three phases:

1. In phase 1, extensive emission characterization would be conducted for production-intent prototype engine and control systems designed to meet 2007 standards for PM and NO_x.
2. In phase 2, extensive emission characterization would be conducted for a group of production-intent prototype engine and control systems meeting the 2010 standards, which require further NO_x reduction (using new types of NO_x control technologies such as selective catalytic reduction or NO_x adsorbers). This characterization will be the basis for selecting heavy-duty diesel engine/aftertreatment system(s) for health testing.
3. In phase 3, a core chronic bioassay of cancer and noncancer endpoints in rats and mice, similar to the standard National Toxicology Program bioassay, would be conducted. In addition to assessing potential carcinogenicity of whole diesel exhaust, the chronic bioassay would provide information on chronic toxicity through histopathologic analyses of multiple organs at interim stages and at the end of the study, on in vivo mutagenicity, and on noncancer health endpoints associated with exposure to diesel exhaust. In addition, selected, established shorter-term respiratory and other noncancer endpoints would be evaluated in shorter exposures after the chronic bioassay.

Assessing the Public Health Impact of Air Quality Actions (Accountability)

Building on the foundation laid out in *Assessing Health Impact of Air Quality Regulations: Concepts and Methods for Accountability Research* (HEI Communication 11, 2003), HEI has issued several RFAs for accountability research and currently has a small number of studies under way. We are also building a much larger base of possible research teams. With new applications for accountability research due in spring 2005, we expect to add several more studies that will make for a more comprehensive accountability program, including much-needed methods development.

Ongoing Research Three accountability studies are under way from RFAs in 2002 and January 2004. They are evaluating health effects of air quality changes such as governmental bans on the sale of coal, changes in former East Germany after natural gas replaced brown coal in power plants and home heating and use of diesel-powered cars and trucks increased, and effects of an urban congestion-charging program intended to reduce traffic and vehicle emissions.

Future Research HEI issued a September 2004 RFA, "Measuring the Health Impact of Actions Taken to Improve Air Quality." This RFA sought applications for studies designed (1) to assess the health effects of actions taken to improve air quality, and (2) to develop methods for conducting such research. HEI is especially interested in evaluation of national actions such as the NAAQS, which are implemented over relatively long time scales; local actions such as state implementation plans; and shorter-term actions such as converting bus systems from diesel to alternative fuels or retrofitting them with control technologies. HEI is also interested in supporting important long-range public health initiatives in areas such as environmental health tracking.

As we focus increasingly on studying the health impact of long-term changes in air quality that result from regulatory or other action, further development and refining of epidemiologic and statistical methods are more critical than ever. Regulatory interventions to improve air quality, especially large national programs such as the US Clean Air Act, may not have immediate effects on either air quality or public health. Ensuing changes in emissions, ambient concentrations, and human exposure may not be demarcated sharply in space or time. And dynamics of biological processes of injury that underlie adverse health effects of air pollution may not directly follow the changes in exposure that result from regulatory action. The longer the time between promulgation of regulations and their effects, the greater the possibility that other risk factors for adverse health outcomes may come into play and interfere with measuring effects of the intervention itself. Developing assessment methods and tracking systems for changes that affect public health (such as medical practice, standard of living, lifestyle, and diet) will be critical for assessing the efficacy of standards and regulations for which changes in emissions play out over a long time. In addition, changes in behavior as a result of improved air quality, such as spending more time outdoors, will need to be taken into account. HEI will continue to build networks with the US Centers for Disease Control and Prevention and state public health tracking programs to facilitate accountability research. HEI will focus on methods to:

- Use data produced by environmental health tracking and surveillance systems to evaluate changes in population health over time in relation to changes in air pollution levels due to actions taken through federal control programs and state implementation plans to meet the NAAQS for PM, ozone, and other pollutants.
- Better measure and integrate into accountability assessments other time-varying factors that may also influence observed changes in health.

Enhanced International Perspective

HEI's efforts to integrate international science into efforts to inform US decisions, and to be cognizant of how that same science can help inform decisions in Europe and other relevant areas, have borne substantial benefit—and will continue in the coming five years. Our initial efforts to bring high-quality and impartial science to bear on international air quality decisions have begun to mature into a modest but sustainable program of targeted research, review, and capacity building, with additional support provided by new public, industry, and government sponsors. Although HEI's core scientific programs will continue to focus on science to inform US decisions, in the next five years HEI will continue this targeted, modest program in international science. Overall, HEI's international efforts will encompass:

- Continued international contributions to HEI's US-focused scientific efforts. This includes the APHENA project (cofunded with the European Union) to bring strong teams from Europe and North America together to test the latest statistical approaches and compare differences in effects across more than 120 cities, as well as other relevant studies of long-term health effects, dose response, and other topics.

- Continuing the PAPA program to build the capacity of Asian scientists to conduct rigorous local health effects studies to inform decisions. In conjunction with the Asian Development Bank and others, the PAPA program will begin to target possible links among air pollution, health, and poverty.
- Conducting limited capacity building with health scientists in other parts of the world to enhance the quality of their research (*e.g.,* Latin America).

Cross-Cutting Issues

HEI will integrate certain cross-cutting issues into its new research. For 2005–2010, we will focus on two susceptible populations at both ends of the age spectrum: fetuses and children and older people. Because senior citizens have become a large fraction of the US population, we need to understand their health risks and how they are influenced by diet, lifestyle choices, medical care, and other factors. In recent years, concern has increased about exposure of children and fetuses to air pollution, in particular developmental effects from exposure in utero.

HEI will also continue to pay attention to basic crosscutting issues laid out in the previous Strategic Plan: (1) exposure assessment; (2) other susceptible groups who are supposed to be protected by air quality standards; (3) mechanisms of toxicity; (4) extrapolation from high to low dose and across species, in order to use information from various studies to understand human health effects at near-ambient pollutant levels; (5) biomarkers for assessing personal exposure, metabolic activation and detoxification, and internal dose of activated compounds; (6) diseases of particular importance that may be affected by multiple pollutants, such as asthma; and (7) methods development, in order to contribute to methods needed to support HEI's research goals.

IMPLEMENTING THE HEI STRATEGIC PLAN 2005–2010

On the basis of extensive comments from HEI sponsors, other stakeholders, and the scientific community, HEI has identified the following activities for implementing the HEI Strategic Plan 2005–2010 according to the timeline in the Figure on page 32.

INNOVATION AND VALIDATION

Over the next five years, HEI will strive to infuse *innovation* and *validation* in everything it does. In a world of rapidly changing science, three key areas of innovation are central:

- Identifying the latest genomics, proteomics, and other tools for health investigation, bringing state-of-the-art practitioners into the field of air pollution and health, and working to validate these emerging tools for health and risk assessments.
- Continuously improving and validating state-of-the art statistical techniques for epidemiologic analysis.
- Increasing Web-based access to data for studies of broad interest.

PRIORITY TOPICS AND TIMETABLE

Over the next five years, HEI will pursue four priority areas that have emerged from initiatives launched in the 2000–2005 Strategic Plan:

- Health effects of the air pollution mixture.
- Emerging technologies.
- Assessing the public health impact of air quality actions (accountability).
- Enhanced international perspective.

Health Effects of Air Pollution Mixture

Building on its efforts on PM, gases, and air toxics, HEI will complete existing projects and build new initiatives that take an increasingly integrated approach to assessing health effects of all pollutants and exposures.

PM and Gases HEI will conduct several activities related to these critical air pollutants.

- Complete, review, and communicate results of existing studies of health effects of PM and gases, including:
  - key current studies of health effects of long-term exposure,
  - animal and human studies of effects of exposure to diesel and other particles on allergic response, and
  - individual studies of mechanisms and health effects of pollutant components.

Major Scheduled Regulatory Events

2005	2006	2007	2008	2009	2010
• US PM NAAQS (staff paper/proposal) • US mobile source air toxics proposal • Euro 5 standards • China, India Euro 3	• PM NAAQS decisions • European CAFÉ ambient standards • US mobile-source air toxics rules • US 15 ppm sulfur diesel	• US highway diesel rules in effect • Ozone NAAQS review • European CAFÉ decisions • US state PM SIPs	• US state PM SIPs • Ozone NAAQS decisions • US utility PM rules	• US state PM SIPs • US nonroad diesel rules begin to take effect • US utility PM rules	Looking ahead • State plans for PM • India, China Euro 4

HEI Strategic Plan 2005–2010

Innovation and Validation

Integrate and validate innovative technologies (eg, genomics, proteomics) in every aspect of HEI work →

Continuous improvement, validation, and data access for state-of-the-art statistics in epidemiology →

Air Pollution Mixture

Toxicity of PM Components, Gases, and Their Sources

Complete key long-term effects, diesel allergy, and mechanism studies—produce HEI Perspectives and consider follow-on studies

Review current science on traffic and health

Systematically investigate toxicity of PM components and sources

Create air and health databases → *Initiate systematic toxicology and epidemiology investigations* →

Air Toxics

Review science on mobile-source air toxics

Air toxics research: *Complete targeted studies of hot spot exposure* →

Air toxics research: *Continue health studies in areas where hot spots identified* →

Understanding the Mixture

Convene workshop and monograph group to examine, synthesize, and recommend innovative approaches to studying health effects of the mixture

Emerging Technologies

Continue tracking emerging technologies: periodic reviews of key issues (eg, alternative fuels, metal and other fuel additives, control technologies) →

ACES

2007 Engines: emission characterization → *2010 Engines: emissions characterization* → *Initiate short-term and chronic testing* →

Measuring Results of Regulation (Accountability)

Continue building networks and alliances with CDC and state public health tracking programs →

Complete initial studies of short-term interventions

Initiate new studies of long- and short-term interventions, new methods development →

Enhanced International Perspective

Complete APHENA and other international studies to inform US and other decisions →

Conduct initial PAPA studies in key Asian cities (including program in air pollution, poverty, and health) → *Publish comprehensive review of Asian science*

- Launch a systematic, multidisciplinary program that will use toxicology, epidemiology, and exposure research to examine and compare toxicity of PM components, gases, and sources.
- Produce new HEI Perspectives on topics including exposure and updated epidemiology findings.
- Conduct an expert review of current and emerging scientific literature of health effects of exposure to traffic.

Air Toxics Recognizing growing interest of agencies, citizens, and others in health effects of air toxics, HEI will continue and extend efforts to assess and investigate exposure to and health effects of key compounds. These efforts will include:

- In the near term, conducting a review and synthesis of current scientific knowledge on exposure to and health effects of major mobile-source air toxics.
- Completing current studies of population exposure to air toxics in potential hot spots (areas likely to have high levels of some air toxics).
- In confirmed hot spots, launching comprehensive studies of health effects.

Understanding Health Effects of the Mixture For decades, scientists have grappled with the best way to assess effects of exposure to a pollutant mixture. To move beyond past efforts, in the spirit in which HEI took on the challenge of laying groundwork for better approaches to accountability, we will convene a workshop and write and publish an expert monograph on developing and implementing innovative approaches to studying health effects of the air pollution mixture.

Emerging Technologies

In keeping with our long-standing mission to track and assess health consequences of emerging technologies and fuels, HEI will work with SCET to:

- Conduct periodic reviews of current knowledge of key technologies (*e.g.,* alternative fuels, metallic fuel additives, and other topics).
- Launch ACES (in collaboration with the Coordinating Research Council and partners in government, industry, and the environmental community) to test 2007 and 2010 heavy-duty diesel engines and fuels.

Assessing the Public Health Impact of Air Quality Actions (Accountability)

Building on HEI Communication 11 (the accountability monograph), we will pursue efforts to improve tracking and assessment of the public health effects of actions taken to improve air quality:

- Completion and communication of results of HEI's initial accountability studies;
- Outreach and support for the development of a sustainable tracking network by state public health agencies and the US Centers for Disease Control and Prevention (who are implementing local and national health tracking systems); and
- Major new research and methods development to assess long-term and short-term effects of domestic air quality actions on public health.

Enhanced International Perspective

HEI's initial efforts to bring high-quality and impartial science to bear on international air quality decisions have begun to mature into a modest but sustainable program with added funds from new public, industry, and government sponsors. In the next five years HEI will continue this focused program in international science by:

- Applying the best science from throughout the world to inform US decisions, for example by completing the APHENA project to test the latest statistical approaches and undertaking other key long-term and dose–response studies.
- Continuing, with additional resources, the PAPA program to build the capacity of Asian scientists to produce rigorous local health effects studies to inform decisions and to begin to target possible links among air pollution, health, and poverty.
- Conducting limited capacity building with health scientists in other parts of the world (*e.g.,* Latin America).

One important element of these modest efforts will be regular communication to HEI's current sponsors of key health and regulatory developments in these international settings.

Cross-Cutting Issues

HEI will attempt to integrate into its programs certain cross-cutting issues, especially health effects of air pollution on two possibly susceptible populations:

- The growing number of elderly in the US population;
- Children (including possible developmental effects after mothers are exposed during pregnancy).

In bringing these cross-cutting issues into its program, HEI hopes to attract a wide range of medical and population health experts who can help place effects of air pollution into the broader context of health issues facing these groups.

APPENDIX B: HEI STUDIES AND RESEARCH REPORTS FROM 1998–2008

RFA 07-1: WALTER A. ROSENBLITH NEW INVESTIGATOR AWARD
Studies under negotiation

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)

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. (2011)

RFA 06-2: ADDITIONAL HEALTH EFFECTS ENDPOINTS DURING THE CHRONIC BIOASSAY
Studies under negotiation

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)

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)

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)

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. (2009)
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. (2009)

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)

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 05-2: 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. (2009)
Qunwei Zhang, University of Louisville
Activation of endothelial cells and gene expression in lungs following exposure to ultrafine particles. (2009)

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. (Completed)
Eric Jordt, Yale University
Pilot study: TRPA1 channels in airway sensory nerve ending as mediators of the irritant effects of acrolein. (Completed)
Debra Laskin, Rutgers University
Pilot Study: 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. (2009)
Junfeng Zhang, University of Medicine and Dentistry of New Jersey
Molecular and physiological responses to drastic changes in PM concentration and composition. (2010)

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 04-2: WALTER A. ROSENBLITH NEW INVESTIGATOR AWARD
Michelle Bell, Yale University
Assessment of the mortality effects of particulate matter characteristics. (2009)
Michaela Kendall, Uludag University
Molecular absorption at PM surfaces; a compelling PM toxicity mediation mechanism. (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. (2007)
James Robins, Harvard School of Public Health
New statistical approaches to semiparametric regression with application to air pollution research. (2009)

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

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. (2008)
Timothy Nurkiewicz, West Virginia University
Pulmonary particulate matter exposure and systemic microvascular function. (2008)

RFPA 04-6: HEALTH EFFECTS OF AIR POLLUTION
Marc Baum, Oak Crest Institute
Significance of highly toxic secondary emissions from on-road vehicles. (2009)
Johannes Filser, GSF-Forschungszentrum für Umwelt und Gesundheit
Pilot study: Quantification of oxidative stress resulting from ambient air; contribution of specified compounds. (Completed)
Ian Kennedy, Uludag University
The uptake of ultrafine particles by vascular endothelial cells and inflammation. (Completed)
Robert Lux, University of Utah
Air pollution effects on ventricular repolarization. (Completed)
John Repine, University of Colorado
Pilot Study: Toxicity of inhaled carbonaceous particles generated under low air-fuel combustion ratio. (Completed)
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. (Completed)
Simon Wong, University of Arizona
Pilot study: The molecular effects of diesel exhaust particulates on respiratory neutral endopeptidase (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)

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. (Completed)
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)

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)

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

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. (Completed)
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. (2009)

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. (Phase 1 Completed; Phase 2: 2008)

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)

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. (Completed)

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)

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 00-1: EFFECTS OF DIESEL EXHAUST AND OTHER PARTICLES ON THE EXACERBATION OF ASTHMA AND OTHER ALLERGIC DISEASES
Richard Effros, Los Amigos Research and Education Institute
Exacerbation of allergic inflammation in the lower respiratory tract by diesel exhaust particles. (2009)
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. (Completed)
George Thurston, New York University
Pilot study: Children's asthma incidence and personal exposures to diesel particles and traffic in New York City. (Completed)
Junfeng Zhang, Environmental and Occupational Health Sciences Institute
Health effects of diesel exhaust in asthmatic patients: a real-world study in a London street. (Completed)

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)

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 98-1: CHARACTERIZATION OF EXPOSURE TO AND HEALTH EFFECTS OF PARTICULATE MATTER
Bert Brunekreef, University of Utrecht
Personal, indoor, and outdoor exposures to $PM_{2.5}$ and its components for groups of cardiovascular patients in Amsterdam and Helsinki. (Report No. 127)
Beverly Cohen, New York University
Field evaluation of nanofilm detectors for measuring acidic particles in indoor and outdoor air. (Report No. 121)
Carole Conn, Lovelace Respiratory Research Institute
Effects of transient exposure to fine particles on host response to influenza. (Study terminated)
Douglas Dockery, Harvard School of Public Health
Association of air pollution with confirmed arrhythmias recorded by implanted defibrillators. (Report No. 124, Part II)
Mark Frampton, University of Rochester
Effects of exposure to ultrafine carbon particles in healthy subjects and subjects with asthma. (Report No. 126)
Henry Gong, Rancho Los Amigos Medical Center
Controlled exposures of healthy and asthmatic volunteers to concentrated ambient particles in metropolitan Los Angeles. (Report No. 118)
Fletcher Hahn, Lovelace Respiratory Research Institute
Particle size and composition related to adverse health effects in aged, sensitive rats. (Report No. 129)
Jack Harkema, Michigan State University
Effects of concentrated ambient particles on normal and hypersecretory airways in rats. (Report No. 120)

Lester Kobzik, Harvard School of Public Health
Effects of combined ozone and air pollution particle exposure in mice. (Report No. 106)
Petros Koutrakis, Harvard School of Public Health
Characterization of particulate and gas exposures of sensitive subpopulations living in Baltimore and Boston. (Report No. 131)
George Leikauf, University of Cincinnati
Pathogenomic mechanisms for particulate matter induction of acute lung injury and inflammation in mice. (Report No. 105)
Christine Nadziejko, New York University
Effect of concentrated ambient particulate matter on blood coagulation parameters in rats. (Report No. 111)
Annette Peters, GSF-Forschungszentrum für Umwelt und Gesundheit
Particulate air pollution and nonfatal cardiac events: air pollution, personal activities, and onset of myocardial infarction in a case–crossover study. (Report No. 124, Part I)
Barbara Turpin, Rutgers University
Contributions of outdoor PM sources to indoor concentrations and personal exposures: a three-city study. (Report 130)
Renaud Vincent, Health Canada
Inhalation toxicology of urban particulate matter: Acute cardiovascular effects in rats. (Report No. 104)

RFPA 98-2: REQUEST FOR PRELIMINARY APPLICATIONS ON THE HEALTH EFFECTS OF EXPOSURE TO AIR POLLUTANTS FROM MOTOR VEHICLE EMISSIONS
Daniel Grosjean, DGA, Inc.
Emissions from diesel and gasoline engines measured in highway tunnels: Airborne carbonyls from motor vehicle emissions. (Report No. 107),
Qingshan Qu, New York University
Genetic susceptibility to benzene hematotoxicity. (Unpublished Report)
Vernon Walker, NYS Department of Health
Genotoxicity of 1,3-butadiene and its epoxy intermediates in mice and rats. (Completed)

RFA 98-3: EPIDEMIOLOGIC INVESTIGATIONS OF HUMAN POPULATIONS EXPOSED TO DIESEL ENGINE EMISSIONS: FEASIBILITY STUDIES
Paolo Boffetta, International Agency for Research on Cancer
Feasibility of an epidemiology study of diesel engine emissions in central Europe and the Commonwealth of independent states. (In HEI Special Report: Research directions to improve estimates of human exposure and risk from diesel exhaust)
Murray Finkelstein, McMaster University
Cancer and diesel exhaust exposure in railroad workers: a feasibility study. (In Special Report)
Eric Garshick, Brigham and Women's Hospital
Lung cancer risk and the quantitative assessment of diesel exhaust exposure in the US trucking industry: a feasibility study. (In Special Report)
David Kittelson, University of Minnesota
Diesel aerosol exposure measurements: a feasibility study. (In Special Report)
Alan Gertler (William Pierson), Desert Research Institute
Emissions from diesel and gasoline engines measured in highway tunnels: Real-world particulate matter and gaseous emissions from motor vehicles. (Report No. 107)
Barbara Zielinska, Desert Research Institute
Diesel emissions exposure measurements in underground mines. (In Special Report)

RFPA 98-4: REQUEST FOR PRELIMINARY APPLICATIONS FOR RESEARCH ON METALS EMITTED BY MOTOR VEHICLES
Thomas Gunter, University of Rochester
A mitochondrial role in manganese toxicity. (Study terminated)
James Schauer, University of Wisconsin
Characterization of metals emitted from motor vehicles. (Report No. 133)
Robert Yokel, University of Kentucky
Manganese toxicokinetics at the blood-brain barrier. (Report No. 119)

RFA 98-5: WALTER A. ROSENBLITH NEW INVESTIGATOR AWARD
Francesca Dominici, Johns Hopkins University
Time-Series Analysis of Air Pollution and Mortality: A Statistical Review. (Report No. 123)

RFPA 98-6: REQUEST FOR PRELIMINARY APPLICATIONS ON THE HEALTH EFFECTS OF AIR POLLUTION
Bert Brunekreef, University of Utrecht
Long-term effects of traffic-related air pollution on respiratory and cardiovascular mortality. (Completed)
Elizabeth Delzell, University of Alabama at Birmingham
An updated study of mortality among North American synthetic rubber industry workers. (Report No. 132)
Alison Geyh, Johns Hopkins University
Evaluation of a Personal and Microenvironmental Aerosol Speciation Sampler (PMASS). (Report No. 122)
Susanne Hering, Aerosol Dynamics
A personal particle speciation sampler. (Report No. 114)

Irva Hertz-Picciotto, University of California at Davis
Early childhood health effects of air pollution. (Unpublished Report)
Daniel Krewski, University of Ottawa
Extended follow-up and spatial analyses of the American Cancer Society study linking particulate air pollution and mortality. (Completed)
Jonathan Samet, Johns Hopkins University
Air pollution and health – a combined European and North American approach. (Completed)
Mark Witten, University of Arizona
Neurogenic responses in rat lungs after nose-only exposure to diesel exhaust.
(Report No. 128)
Scott Zeger, Johns Hopkins University
Internet health and air pollution surveillance system. (Communication 11)
Barbara Zielinska, Desert Research Institute
Atmospheric transformation of diesel emissions. (Completed)

APPENDIX C: HEI SPECIAL QUALITY ASSURANCE PROCEDURES

I. Policy Statement

It is the policy of the Health Effects Institute to utilize special quality assurance (QA) procedures for research projects that may produce data of regulatory significance. These procedures augment the QA/QC procedures applied to all HEI studies and provide assurance that data are collected under defined conditions and are reliable and traceable. This will aid in assuring that conclusions drawn from the data are scientifically valid. If there is a QA program in place at the institute at which the research is being conducted, then HEI will assess its adequacy and modify its QA procedures as necessary.

Quality assurance is achieved through six basic components:

A. Use of a written protocol

B. Use of written standard operating procedures

C. Involvement of qualified personnel

D. Maintenance of written records

E. Use of appropriate data processing techniques

F. Use of quality control procedures for all data collected

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

II. QUALITY ASSURANCE COMPONENTS

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

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

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

B. *Written standard operating procedures* (SOPs) will be used to document all routine, critical experimental procedures and measurement techniques for which variability must be minimized. Critical experimental procedures are those procedures that result in the acquisition of experimental samples or data used to draw scientific conclusions.

Standard operating procedures will be developed by individuals knowledgeable of the specific procedures. They will describe what, when, where, how, and why in a stepwise manner. They will be sufficiently complete and detailed to ensure that the data collected are of known and documented quality and integrity and are generated to meet measurement objectives such that there is a minimum loss of data due to out-of-control conditions.

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

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

Standard operating procedures will be:

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

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

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

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

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

The Principal Investigator for the project shall periodically, at not less than biweekly intervals, review the records to verify their completeness and accuracy. This review shall be documented by the Principal Investigator signing and dating the reviewed record.

E. *Documented procedures* will be used to assure the integrity and appropriateness of data processing procedures. Data processing includes all manipulations performed on raw, (i.e. "as collected") information to change its form of expression, its location, or its quality. This includes data collection, validation, storage, transfer, reduction, and analysis.

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

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

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

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

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

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

6. Data analysis
   Data analysis frequently includes computation of summary statistics and their standard errors, confidence intervals, tests of hypotheses relative to the parameters, and model validation (goodness of fit tests). The protocol will address the specific statistical procedures to be used, the reliability of computations, appropriateness of the models as a framework for investigating the study questions and robustness of statistical procedure to model inaccuracies.

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

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

   a. Replicate samples
      Replicate sample data shall be within predetermined acceptance limits.

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

   Examples of checks include:
   (1) Zero and span
   (2) Noise levels
   (3) Drift
   (4) Flow rate
   (5) Linearity

2. Accuracy

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

a. Traceability of instrumentation

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

b. Traceability of standards

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

c. Traceability of samples

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

d. Traceability of data

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

e. Methodology

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

f. Reference or spiked samples

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

3. Representativeness

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

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

4. Comparability

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

Examples are:

a. Consistency of reporting units

b. Standardized setting, sampling, and analysis

c. Standardized data format

III. ROLES OF INSTITUTIONS AND INDIVIDUALS IN ACHIEVING QUALITY ASSURANCE

A. Health Effects Institute

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

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

B. Project Personnel

1. Principal Investigator

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

The Principal Investigator has the responsibility for the actual conduct of the research according to the protocol and SOPs. He or she has the primary responsibility of managing all aspects of data collection, validation, storage, transfer, reduction, and analysis. The Principal Investigator has the responsibility for assuring that the research is conducted with qualified personnel and in accordance with this quality assurance plan.

2. Professional personnel

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

3. Technical and supporting personnel

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

C. Special QA Oversight

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

The Special QA Officer may conduct periodic audits of the research while in progress and when it is completed to ascertain compliance with the HEI's special QA procedures. These audits shall include such matters as review of research procedures, notebooks, data forms, and data management activities. At the conclusion of each audit, the QA Officer shall provide a verbal summary to the Principal Investigator of significant findings that need to be addressed. The QA Officer shall also prepare a "Business Confidential" report of the audit. The report shall detail the nature of the audit significant findings, and any requirements for corrective action(s). The audit report shall be provided to the HEI Director of Science, who will then transmit it to the HEI project manager for transmission to the Principal Investigator. If corrective action is required, the Principal Investigator shall see that such action is taken and return the summary to the HEI project manager with a copy to the QA Officer noting the action taken. All copies of the audit report are to be marked as "Business Confidential" and are to be destroyed after use or maintained in a file separate from other records of the project. These audit reports are only to be released to people directly involved in management of the projects. To give these reports to people who are not directly involved violates the confidential nature of the audits and potentially reduce the degree of candor required in communications within the project on matters requiring corrective action. The QA Officer shall maintain a log of all audits indicating for each audit: the date conducted, participating personnel, and the nature of the audit.

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

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

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

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

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

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

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

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

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

5. *Responsibility of the Data Requester* In addition to the payment of reasonable costs and the obtaining of any necessary confidentiality approvals, HEI will ask the data requester, as would be normal courtesy in the scientific

community, to inform both the Principal Investigator and HEI of any findings emerging from their analysis, to provide the Principal Investigator an opportunity to respond to those findings prior to publication, to provide copies to both the Principal Investigator and HEI of any papers submitted for publication from the data, and to cite both HEI and the Principal Investigator in any publication, noting explicitly that the views expressed are those of the new analyst and not those of the Principal Investigator, HEI, or HEI's sponsors.

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

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

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