Request for Applications

HEALTH EFFECTS INSTITUTE

December 2014

Fall 2014 Research Agenda

RFA 14-3 Assessing Adverse Health Effects of Long-Term Exposure to Low Levels of Ambient Air Pollution

RFA 14-4 Walter A. Rosenblith New Investigator Award

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

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

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

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

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

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[1] Section has been revised since the previous Winter 2014 RFA booklet

[2] A revised draft Strategic Plan for 2015-2020 can be found on the HEI website. A final Plan will be available in April 2015.

INTRODUCTION

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

REQUEST FOR APPLICATIONS 14-3: ASSESSING ADVERSE HEALTH EFFECTS OF LONG-TERM EXPOSURE TO LOW LEVELS OF AMBIENT AIR POLLUTION

RFA 14-3 solicits studies to analyze and evaluate exposure-response function(s) for $PM_{2.5}$ and other pollutants at levels currently prevalent in North America, Western Europe and other high-income regions and related questions about adverse health effects at low levels of ambient air pollution. In addition, RFA 14-3 solicits studies to develop methods required for, and specifically suited to, conducting such research. At the outset, HEI expects to fund a small number of large studies for up to 4 years. HEI also expects to fund some smaller-scale methods development studies.

The submission and review of applications for RFA 14-3 will entail a two-stage process:

- Interested scientists should submit a preliminary application by **FEBRUARY 16, 2015**. The HEI Research Committee and outside consultants will discuss the preliminary applications and will provide feedback within 4 weeks after submission.
- Full applications (by invitation only) should be submitted no later than **JULY 13, 2015**. Full applications will be discussed by the Research Committee in October 2015.

REQUEST FOR APPLICATIONS 14-4: WALTER A. ROSENBLITH NEW INVESTIGATOR AWARD

The purpose of this award, described on pages 17–18, is to bring new, creative investigators into active research on the health effects of air pollution. It provides three years of funding to an investigator with outstanding promise at the Assistant Professor or equivalent level for a small project relevant to HEI's research interests. For information on HEI's current research priorities, applicants should consult *Appendix A*, which contains an overview of HEI's upcoming Strategic Plan for 2015-2020. (The final Strategic Plan will be posted on the HEI website in April 2015 when it will go into effect.)

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

- Interested scientists should submit a Letter of Intent and Curriculum Vitae by **MARCH 2, 2015**.
- Full applications should be submitted no later than **APRIL 6, 2015**.

THE HEALTH EFFECTS INSTITUTE

WHAT IS HEI?

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

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

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

HOW DOES HEI WORK?

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

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

During the course of each study, the Research Committee and scientific staff maintain close contact with HEI-funded investigators by means of progress reports, site visits, workshops, and the HEI Annual Conference. The 10-month progress report serves as the basis for contract renewal for multi-year projects. A site visit is conducted to many investigators' laboratories, not only to assess the conduct of the study, but also to provide an opportunity for discussion and exchange of ideas. At the Annual Conference, HEI investigators, Research Committee and Review Committee members, HEI staff, representatives of sponsor organizations, invited scientists, and other attendees meet to share information and develop new ties to strengthen the HEI community of scholars. A more detailed description of the relationship between HEI and investigators can be found on pages 25–29.

In order to fulfill its mission of providing timely, high-quality research results for decision makers, HEI has developed a rigorous review process to evaluate results of the research it funds. When a study is completed, the investigator is required to submit a comprehensive final report. The HEI Review Committee, which has no role in the review of applications or in the selection or conduct of projects, assesses the scientific quality of each completed study and evaluates its contribution to unresolved scientific questions. The investigator's Final Report and a Commentary of the Review Committee are published together by HEI. Additionally, all HEI investigators are urged to publish the results of their work in the peer-reviewed literature. More information on the final report and review process can be found on pages 27–28.

THE HEI RESEARCH PROGRAM

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

In April 2014, HEI issued a draft of the new five-year plan, the *HEI Strategic Plan for Understanding Health Effects of Air Pollution 2015–2020*, which describes research and review priorities and plans for implementing them. In October 2014, a revised Plan was circulated. A final Plan is expected to be issued in April 2015. Here, we provide a brief overview of the four priority areas included in the new five-year Plan.

Challenging air quality standards decisions continue to arise around the globe as science evolves and as societal needs change. Given that, the HEI Strategic Plan 2015-2020 is built around one overarching theme:

Informing Air Quality and Climate Technology Decisions for 2015 – 2020…and Beyond."

HEI sees this broad theme integrated into four core program elements: (1) the continuing challenges of **multipollutant science**; (2) **accountability and transparency**; (3) assessing **emerging fuels and technologies**; and (4) and **global health science**. In each of these areas, HEI has described detailed plans for its research and other scientific activities, including:

- Completing and communicating the results of key studies on ozone and cardiovascular effects, traffic exposure, diesel, accountability, and other important topics.
- Launching major new research initiatives including, among others:
  - Examining potential effects at the lowest levels of exposure
  - New targeted studies of the health effects of traffic exposure
  - Rigorous side-by-side, short term health testing of key fuel/technology combinations
- The next generation of accountability studies of major air quality actions, and
- With additional funds, new source-specific assessment of air pollution health impacts in developing countries.
- Pursuing, across our work, important **cross-cutting issues** in all of our efforts.

For more detailed information, please refer to *Appendix A* and to the revised draft Strategic Plan 2015-2020 posted on the HEI website.

RFA 14-3: ASSESSING ADVERSE HEALTH EFFECTS OF LONG-TERM EXPOSURE TO LOW LEVELS OF AMBIENT AIR POLLUTION

INTRODUCTION

The Health Effects Institute (HEI) is seeking to fund studies to assess health effects of long-term exposure to low levels of ambient air pollution, including studies to evaluate all-cause and cause-specific mortality and morbidity endpoints. Request for Applications (RFA) 14-3 solicits studies to analyze and evaluate exposure-response function(s) for $PM_{2.5}$ and other pollutants at levels currently prevalent in North America, Western Europe, and other high-income regions, and related questions about health effects associated with long-term exposure to low levels of ambient air pollution. In addition, RFA 14-3 solicits studies to develop methods required for, and specifically suited to, conducting such research.

Before funding full studies, HEI seeks to determine whether potential studies are feasible and likely to meet the stated objectives. Therefore, HEI requires that all respondents to this RFA first submit a preliminary application, so that the HEI Research Committee and outside consultants may evaluate their feasibility. Subsequently, applicants will be informed whether or not to submit a full application. Details can be found in the section *Application Process, Deadlines, and Evaluation*.

BACKGROUND AND RATIONALE

Levels of ambient air pollution have generally declined over several decades in North America, Western Europe, and other high-income regions, due in large part to air quality regulation and subsequent improvements in vehicular technology and industry, although at the same time, some population groups in high-income countries are still exposed to higher levels of air pollution, for example, as a consequence of living close to major roads and other major sources. Current $PM_{2.5}$ annual average air quality standards are 12 and 25 $\mu g/m^3$ in the US and Europe, respectively. The WHO's worldwide current annual average $PM_{2.5}$ air quality guideline is 10 $\mu g/m^3$.

Epidemiologic studies have reported associations of air pollution with health effects in the general population even at levels below current air quality standards. Recent cohort studies that have provided $PM_{2.5}$-related mortality estimates are listed in Table 1. $PM_{2.5}$ exposure estimates in most studies were between 6 and 30 $\mu g/m^3$. They generally observe increased risk of all-natural and cause-specific mortality from chronic disease, although the estimates vary in size, especially with regard to cause-specific mortality, for reasons that are largely unexplained. Using the estimates from these studies in risk assessments of mortality and loss of healthy years of life attributable to air pollution leads to large estimates of attributable burden. The recent Global Burden of Disease (GBD) 2010 project estimated that 3.2 million premature deaths in 2010 worldwide were attributable to PM outdoor air pollution, with 103,027 and 165,598 premature deaths in the US and Western Europe, respectively (Lim et al. 2012). Estimates vary depending on the shape of the exposure-response function used, and particularly on assumptions made as to its form at both low and high concentrations of air pollution. For example, GBD 2010 assumed no $PM_{2.5}$-related effects below ~5 $\mu g/m^3$, because the cohort studies underlying these estimates did not provide reliable information below that level (Lim et al. 2012; Burnett et al. 2014).

The United States Environmental Protection Agency (US EPA) has used a variety of approaches for the estimation of risks at low levels of ambient air pollution in the National Ambient Air Quality Standard reviews, regulatory impact analyses, and burden assessments, reflecting shifting views within the scientific community regarding the shape of the concentration-response relationship and appropriate methods to reflect differences in the degree of confidence in risk estimates at low concentrations. The current approach used by the US EPA, consistent with the most recent versions of the Integrated Science Assessments for $PM_{2.5}$ and ozone, is to estimate risks for the full range of ambient concentrations experienced by populations, with no assumed threshold or lower bound. These estimates are accompanied by a discussion of the uncertainties associated with risk estimates at lower concentrations where the density of air quality data is lower. (US EPA 2009; US EPA 2010; US EPA 2013).

The scientific evidence for effects at levels below current air quality standards, the large estimates of the air pollution-attributable burden of disease, as well as the interest in reducing greenhouse gases, suggest that more stringent air quality standards and guidelines may be considered in the future. For these reasons, there is a need for additional investigation to improve our understanding of exposure-response function(s) for mortality and morbidity at low levels of $PM_{2.5}$, ozone, and other ambient air pollutants. Such studies would inform risk assessors and policy makers regarding exposure-response functions at levels of ambient air pollution currently prevalent in North America, Western Europe and other high-income regions.

OVERALL OBJECTIVES OF RFA 14-3

1. Fund studies to assess health effects of long-term exposure to low levels of ambient air pollution, including all-cause and cause-specific mortality and morbidity endpoints. Studies should analyze and evaluate exposure-response function(s) for $PM_{2.5}$ and other pollutants at levels currently prevalent in North America, Western Europe, and other high-income regions and may also address related questions about health effects at low levels of ambient air pollution.

2. Develop statistical and other methodology required for, and specifically suited to, conducting such research including, but not limited to, evaluation and correction of exposure measurement error.

SPECIFIC OBJECTIVES OF RFA 14-3

1. Compare and contrast alternative models and their uncertainty, e.g., threshold/non-threshold, linear/non-linear, and parametric/non-parametric, to characterize the exposure-response function(s) at low levels of ambient air pollution.
2. Explore possible variability in effect estimates at low levels among populations, and identify possible contributing factors. Such factors may include age, socio-economic position, health status, and access to medical care, as well as differences in air pollution sources and time-activity patterns.
3. Develop and evaluate exposure assessment methods suitable to estimate exposure to low levels of air pollution at various spatial and temporal scales in large study populations, including populations who reside in areas not covered by routine ground-level monitoring.
4. Develop, evaluate, and apply statistical methods to quantify and correct for exposure measurement error in risk estimates and in characterization of exposure-response relationships.
5. Develop and validate approaches to assess the impacts of co-occurring pollutants on health effect associations at low ambient concentrations.
6. Develop and validate indirect approaches to correct risk estimates for the effects of important potential confounding variables, such as smoking, in the absence of such data at the individual level.
7. Improve techniques for record linkage and methods for disclosure protection for optimal use of large administrative databases in air pollution and health research.

HEI encourages applicants to address more than one specific objective, if feasible, within the budget constraints.

CRITICAL STUDY DESIGN CONSIDERATIONS

To inform the development of RFA 14-3, the HEI Research Committee held a workshop in June 2014 with selected participants from the research and regulatory communities and the private sector. A number of considerations pertinent to study design issues discussed during the workshop are summarized below. The ability to address and integrate these considerations will be central to the funding decision.

Study populations. Large studies — as large as, or larger than, existing studies — will be needed to address the overall objectives with regard to the amount of exposed person-time at low levels of $PM_{2.5}$ and other pollutants. This could be accomplished via consortia combining existing studies, or by using data from very large populations obtained from, for example, administrative databases, such as census data or health insurance programs. A recent example of a study combining existing cohorts is the European Study of Cohorts for Air Pollution Effects (ESCAPE) study in which common exposure metrics — derived from a detailed measurement campaign, and land use regression modeling — were applied to diverse general population cohorts; subsequently the cohort-specific results were combined via meta-analytic techniques and corrected

for important (individual) level confounders such as smoking (see, for example, Beelen et al. 2013, Table 1). Alternatively, the data from multiple cohorts could be combined in one pooled analysis. A few examples exist of very large cohort studies using administrative databases (see e.g., Crouse et al. 2012, Zeger et al. 2008, Table 1). Crouse et al. (2012) assembled a 2.5 million-person cohort with relatively low exposure levels using Canadian Census data. The two design options are not mutually exclusive, and there may be alternative design options to address the overall objectives.

Both design options have their strengths and limitations. Strengths of cohort studies are that they typically collect detailed information on important potential confounders at the individual level; strengths of studies using administrative databases are that they can cover very large and 'representative' populations. Limitations of cohort studies may include that detailed information is only available at baseline, and that study populations may not be representative of general populations or specific sub-populations thereof. Drawbacks of using administrative databases include that relatively little information may be available on important potential confounders at the individual level, and record linkage may be challenging. Applicants designing studies should discuss the specific limitations of their study design and develop approaches to address them. Given the increasing demands on the broader scientific and policy communities to make datasets publically available — while maintaining confidentiality — studies that would improve techniques for record linkage and methods for disclosure protection would be of value.

In addition, smaller-scale studies that develop methods will be considered responsive, provided that the applicants make a strong case that such methods are applicable to study designs pertinent to RFA 14-3.

Geographic location. Studies in North America, Western Europe, and other high-income regions characterized by relatively low ambient air pollution levels would be considered responsive. Studies in other regions of the world will be considered, provided that the study includes sufficient exposed person-time at or near levels currently prevalent in high-income regions.

Exposure assessment. Studies should develop and evaluate methods to estimate exposure of large populations at relevant spatial and temporal scales in geographic areas characterized by relatively low ambient concentrations. In most cohort studies to date, exposure estimates have been based on residential proximity to routine ground-level air pollution monitors. The existing monitoring networks — even those in North America and Western Europe — have limited spatial coverage with typically few stations in suburban and rural locations. As a consequence, most cohorts to date focused on urban populations. In addition, most existing monitoring networks have insufficient density to capture small-scale (within-city) variation of air pollution, which can be quite substantial for certain pollutants (e.g., Cyrys et al. 2012; Eeftens et al. 2012).

Recent developments in satellite-based remote sensing, and other exposure methods and models (e.g., land use regression models and 'hybrid' models combining satellite data and land use regression models), and improvements in the quality and coverage of ground-level measurements have shown potential to provide air pollution estimates that cover large areas in a country, whole countries, or even multiple countries, with a sufficiently high degree of spatial resolution. These improvements allow exposure to potentially be estimated for large populations, including populations exposed to low levels of air pollution (e.g., Beckerman et al. 2013; Beelen et al. 2009; Hart et al. 2009; Novotny et al. 2011). Applicants will need to validate air pollution exposure estimates, in particular for the lower levels of exposure and when new methods and models are applied. Applicants should consider the design of the exposure assessment, and its requisite level of complexity, with regard to its ultimate effect on the accuracy and precision of the health effect estimates (Szpiro et al. 2011; 2013).

All studies should estimate exposure to $PM_{2.5}$ and preferably also include other criteria pollutants, such as NO_2, O_3, or other pollutants of interest (such as $PM_{2.5}$ components), especially when exposure will be assessed at different spatial scales including a within-city component. Applicants should, to the maximum extent possible, consider multi-pollutant modeling approaches to estimate effects of pollutants that are often highly correlated (see for a review, for example, Johns et al. 2012).

Applicants should make explicit, and justify, their choice of induction time(s) between exposure and health effects. Studies with the potential of characterizing exposure at different time scales to identify induction times would be of value.

Applicants proposing a study design that combines existing studies will need a common methodology to characterize exposure. Comparison between results from air pollution cohort studies to date is often hampered because the studies differ in the spatial scale of the exposure assignment.

Exposure measurement error — a potential source of bias in all epidemiologic studies (e.g., Sheppard et al. 2012) — is a particular challenge when assessing health effects of long-term exposure to low levels of ambient air pollution where effect sizes are expected to be relatively small. Therefore, studies should quantify exposure measurement error, and, if possible, adjust for it. Estimating exposure using nearest monitor to the residence typically results in underestimation of exposure, and models predicting outdoor concentrations at the residence better reflect personal exposure to ambient concentrations (e.g. Kioumourtzoglou et al. 2014). Moreover, residential mobility can affect long-term exposure of study subjects; ignoring residential mobility could potentially introduce substantial exposure measurement error (e.g., Hystad et al. 2012). Finally, the variability of individual time activity patterns, and longer term changes in those patterns, may further contribute to error. Proposed studies should take into account these potential sources of error in the exposure assessment, if possible, for all potential effects, and especially for effects with long induction times such as lung cancer.

Health outcomes. Health effects of interest are all-cause and cause-specific mortality and morbidity endpoints. Inclusion of additional health endpoints, such as adverse pregnancy outcomes, lung function, and well-established clinical markers of disease will be considered responsive.

If a proposal combines existing studies, a common methodology for effect assessment will be necessary. A common strategy for classifying and grouping adverse outcomes will be needed as well.

Control for important potential confounders. Studies need to control air pollution risk estimates for major potential confounders (e.g., smoking, socio-economic status) either by restriction or by direct or indirect adjustment approaches.

Studies using administrative databases typically include individual level information on age, sex, and race, but may not include important individual-level information on lifestyle risk factors, such as smoking habits, diet, alcohol consumption, or socio-economic status. If such a study is proposed, indirect approaches need to be developed and validated to correct risk estimates for important potential confounding variables, in the absence of such data at the individual level (Rothman et al. 2008). Indirect approaches have been used to correct for those factors in the analyses using, for example, standardized mortality ratios for COPD (e.g., Zeger et al. 2008), or using pre-existing comorbidities of COPD, diabetes, and hypertensive heart disease (e.g., Cesaroni et al. 2013). Using those alternative approaches requires careful consideration because comorbidities might act as intermediate variables. In addition, other approaches — typically used to control for confounders at a more aggregated (neighborhood) level — exist to control for various important confounders.

Precision and statistical power. Studies should be designed to maximize the number of people exposed at the low end of the exposure range, while also including sufficient people in the 'middle' or 'higher' end of the exposure range in geographic areas characterized by relatively low ambient concentrations. As a general guideline, current $PM_{2.5}$ annual average air quality standards from the US and Europe can be considered as the maximum value of what can be considered 'low' levels.

Applicants should assess and discuss the expected precision and statistical power of their estimates with regard to 1) whether risks at low levels can be detected and at what concentrations and 2) whether different models to characterize the exposure-response function(s) at low levels can be reliably distinguished. Assumptions needed for such calculations should be guided by previous relevant literature. Calculations should include some discussion of the influence of exposure measurement error.

METHODS DEVELOPMENT

RFA 14-3 also solicits proposals to develop methods required for, and specifically suited to, conducting research to assess adverse health effects of long-term exposure to low levels of ambient air pollution, either as part of a full study or as a stand-alone study. Examples of currently needed methods development and refinement include:

- Methods to quantify and correct for exposure measurement error in risk estimates.
- Multi-pollutant modeling approaches to estimate effects of pollutants that are often highly correlated.
- Opportunities to develop and validate alternative causal modeling approaches for application in such studies.

- Exposure assessment methods suitable to estimate exposure to low levels of air pollution in large study populations, including populations in areas not covered by routine ground-level monitoring. This may include comparing the performance of exposure assessment methods that differ in the spatial scale of the exposure assignment (e.g., city, zip code, or address), and characterizing exposure at different time scales to identify induction time(s).

This may also include validating exposure based on complex exposure models and remote sensing measurements.

- Methods for indirect approaches to correct risk estimates for the effects of important potential confounding variables, such as smoking.
- Techniques for record linkage and methods for disclosure protection for optimal use of large administrative databases in air pollution and health research. When using large administrative databases, such as the US Census, maintaining confidentiality will be especially important.

FUNDING AVAILABLE

Overall, a total of $5 to $6 million will be available under RFA 14-3. At the outset, HEI expects to fund a small number of large studies for up to 4 years. HEI also expects to fund some smaller-scale methods development studies.

POLICY ON DATA ACCESS

Providing access to data is an important element in ensuring scientific credibility, and is particularly valuable when studies are of regulatory interest. 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* can be found in Appendix D (pages 53-54).

Applicants selected to submit full applications will be expected to include a plan for data sharing and accessibility at the end of the study. Where data are provided by a third party, a process for other investigators to obtain and work with the data should be outlined.

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Table 1 Recent Cohort studies of $PM_{2.5}$ and mortality

Cohort	**Country**	**Study population**	**Study size (number of total deaths)**	**Follow up years**	**Mean $PM_{2.5}$in µg/m³ (minimum-maximum)**	**Spatial scale***	**Reference**
Cohort studies							
Agricultural Health Study Cohort (AHS)	US	Farmers, spouses, and commercial pesticide applicators in Iowa and North Carolina	83,378 (5,931)	1993-2009	10 (SD=2)	Address (satellite, 10 km grid)	Weichtenthal et al. 2014
American Cancer Society (ACS)	US	Adults from 51 cities	499,968 (NA)	1982-2000	14.0 (6-22)	City	Krewski et al. 2009
Adventist Study of Health and Smog (AHSMOG)	US	Californian seventh-day Adventists	3,239 (250 for CVD)	1977-1998	29 (SD=10)	Address (interpolation)	Chen et al. 2005
California teachers	US	Female teachers in California	101,784 (4,147)	1997-2005	16 (3-28)	Address (interpolation)	Lipsett et al. 2011
Dutch Study on Diet and cancer (NLCS-AIR)	Netherlands	Elderly subjects	120,852 (17,286)	1987-1996	28 (23-37)	Address (LUR)	Beelen et al. 2008
Harvard Six city	US	Adults in 6 cities	8,096 (4,495)	1974-2009	16 (11-24)	City	Lepeule et al. 2012
Health Professionals	US	Highly educated men in Midwestern and northeastern states	17,545 (2,813)	1989-2003	18 (SD=3)	Address (LUR)	Puett et al. 2011
Japanese Cohort	Japan	Adults from 6 areas	63,520 (6,687)	1985-1995	17-42 (average of different cities) (SD=NA)	City	Katanoda et al. 2011
National English Cohort	UK	Primary care adult patients	835,607 (83,103)	2003-2007	13 (9-20) (2002 only)	Zip code (dispersion, 1 km grid)	Carey et al. 2013
Nurses Health	US	Women from northeastern metropolitan areas	66,250 (3,785)	1992-2002	14 (6-28)	Address (LUR)	Puett et al. 2009
US truckers	US	Men in trucking Industry	53,814 (4,806)	1985-2000	14 (SD=4)	Address	Hart et al. 2011
Veteran's study	US	Male veterans	23,872 (7,386)	1997-2001	14.3 (SD=3)	County	Lipfert et al. 2006
Women's Health Initiative (WHI)	US	Postmenopausal women from 36 metropolitan areas	65,893 (1,816 for CVD)	1994-1998	13.5 (3-28)	Zip code	Miller et al. 2007

Table 1 continued

Cohort	Country	Study population	Study size (number of total deaths)	Follow up	Mean $PM_{2.5}$ in µg/m3 (min-max)	Spatial scale*	Reference
Very large cohort studies, or combining existing cohorts							
Canadian national cohort	Canada	Nonimmigrant adults	2.1 million (200,000)	1991-2001	9 (2-19)	Enumeration area (satellite, 10 km grid)	Crouse et al. 2012
European Study of Cohorts for Air Pollution Effects (ESCAPE)	22 European cohorts (in 13 countries)	General population samples	367,251 (29,076)	1985-2007	7-31 (average of SDPP cohort in Sweden, and the SIDRIA cohort, Italy) (SD: 1.3-1.7)	Address (LUR)	Beelen et al. 2013
Medicare cohort	US	Elderly (>=65 years old) Medicare recipients	13.2 million (4.88 million)	2000-2005	13 (SD=4)	Zip code (within 6 miles of a monitor)	Zeger et al. 2008
New Zealand Census Study	New Zealand	Urban areas	1.06 million (17,937)	1996-1999	8 (0.1-19)**	Census tract area (dispersion)	Hales et al. 2012
Rome cohort	Italy	Adults in Rome	1.3 million (144,441)	2001-2010	23 (7-32)	Address (dispersion, 1 km grid)	Cesaroni et al. 2013

Abbreviations: CVD = cardiovascular disease; LUR = land use regression model; NA=not available; PM= particulate matter; SD= standard deviation; UK = United Kingdom; US = United States; *Spatial scale of exposure assignment; ** PM_{10}

RFA 14-3: APPLICATION PROCESS, DEADLINES, AND EVALUATION

The submission and review of applications for RFA 14-3 will entail a two-stage process: a preliminary application followed by a full application (upon request only). Full applications without pre-submission of a preliminary application will **not** be considered.

PRELIMINARY APPLICATION

Before funding full studies, HEI seeks to determine whether potential studies are feasible and likely to meet the stated objectives. Therefore, HEI requires that all respondents to this RFA first submit a preliminary application. In addition to a description of design features (e.g., study population, locations, exposure assessment approach, number of events, person-time exposed [if available]), applicants should provide a preliminary assessment of expected precision and power to support the proposed study. In addition, a brief description of the scientific rationale, study aims, statistical analyses, and anticipated results should be included.

Applicants proposing a study to develop methods should also submit a preliminary application and make the case that those methods are applicable to study designs pertinent to RFA 14-3.

Preliminary applications should include an estimated total budget and study duration. In addition, brief curricula vitae (CVs; maximum 2 pages per person) of the principal investigator and co-investigators should be provided.

Applicants should use the Preliminary Application Form, which can be downloaded from *www.healtheffects.org/funding.htm*. The preliminary application must be no more than seven pages in length (using 11-point font size and 1-inch margins; excluding references and CVs).

Deadline for Preliminary Applications

Preliminary applications should be submitted by e-mail in PDF format to *funding@healtheffects.org* no later than **FEBRUARY 16, 2015**. HEI will acknowledge receipt of the application.

Preliminary Application Evaluation Process

Preliminary applications will be reviewed by the Research Committee and outside consultants. They will decide whether 1) full applications are warranted, 2) other population(s) and/or researcher(s) needs to be added to the proposal and 3) whether the different preliminary applications received would best be combined under a common protocol for characterizing exposure and health analyses. Applicants will be informed whether or not to submit a full application within 4 weeks after the submission date.

For questions contact: Dr. Aaron Cohen (*acohen@healtheffects.org*, +1-617-488-2325) or Dr. Hanna Boogaard (*jboogaard@healtheffects.org*, +1-617-488-2306).

FULL APPLICATION

Invited full applications should provide in-depth information on aspects presented in the preliminary application: the study aims, design, rationale, methods, and statistical analyses. If data from other studies are going to be used, information on the type of data available (including the period, location, and frequency of when the measurements were taken) and quality assurance should be included. Applicants should also discuss whether they will need to obtain IRB approval. A letter from the investigator who owns the data should be submitted, stating his or her willingness to share the data with the applicant and with HEI, if requested (see Appendix D: *HEI Policy on the Provision of Access to Data Underlying HEI-funded Studies* on pages 53-54). In addition, the full application should include a plan for data sharing and accessibility at the end of the study.

Investigators invited to submit a full application should use forms F-1 to F-12 (see list on page 37) and consult the *Instructions for Completing the Application* found on pages 31-36. Application forms can be downloaded from *www.healtheffects.org/funding.htm*. Please note that the required font size is **11 point with 1-inch margins**.

Deadline for Full Applications

Full applications should be submitted to *funding@healtheffects.org* no later than **JULY 13, 2015**. The application should be in PDF format with a maximum file size of 20 MB. HEI will acknowledge receipt of the application.

Full Application Evaluation Process

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

EXTERNAL REVIEW

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

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

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

INTERNAL REVIEW

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

RFA 14-4: WALTER A. ROSENBLITH[1] NEW INVESTIGATOR AWARD

INTRODUCTION

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

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

HEI RESEARCH PROGRAM

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

In considering potential research topics, applicants should be aware of HEI's current areas of interest, as described in a revised draft of the HEI Strategic Plan for 2015-2020 (see *Appendix A*). A final version is expected to be published in April 2015. The focus is on four key areas: (1) addressing challenges of multi-pollutant science, (2) health outcomes and transparency, (3) emerging fuels and technologies, and (4) global health science.

Appendix A includes sections of the Strategic Plan 2015-2020 that describe HEI's current research priorities and plans for implementing them. The revised draft of the Strategic Plan 2015-2020 is available on HEI's website, *www.healtheffects.org/funding.htm*. Appendix B provides a listing of HEI studies and reports, which gives information on the pollutants and issues in which HEI has been interested over the years.

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

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

HEI encourages investigators to submit applications addressing these high priority research areas. However, HEI realizes that other areas of research may lead to results important to its mission. For this reason, we will also consider particularly innovative or high quality applications in other areas that are relevant to the overall goals of HEI's program.

LIST OF AWARDEES

Year	*Awardee and Project Title*
1999	Francesca Dominici, Johns Hopkins University, Air pollution and daily mortality in a national sampling frame
2001	Quanxin Meng, Battelle Toxicology Northwest, Mutagenicity of stereochemical configurations of 1,3-butadiene epoxy metabolites in human cells
2002	Jamie Schauer, University of Wisconsin, Source apportionment and speciation of particulate matter to support exposure and health studies
2003	Michael Borchers, University of Cincinnati, T cell subpopulations regulate airway inflammation and injury following acrolein exposures
2004	Michelle Bell, Yale University, Assessment of the mortality effects of particulate matter characteristics
2004	Michaela Kendall, Uludag University, Turkey, Molecular adsorption at PM surfaces: a compelling PM toxicity mediation mechanism
2005	Jonathan Levy, Harvard School of Public Health, Using geographic information systems to evaluate heterogeneity in indoor and outdoor concentrations of particle constituents
2005	Timothy Nurkiewicz, West Virginia University, Pulmonary particulate matter exposure and systemic microvascular function
2006	Christopher Paciorek, Harvard School of Public Health, Integrating monitoring and satellite data to retrospectively estimate monthly $PM_{2.5}$ concentrations in the eastern United States
2006	Qunwei Zhang, University of Louisville, Activation of endothelial cells and gene expression in lungs following exposure to ultrafine particles
2007	Charles Stanier, University of Iowa, Development and application of a personal exposure screening model for size-resolved urban aerosols
2007	Yifang Zhu, Texas A&M University Kingsville, Assessing children's exposure to ultrafine particles from vehicular emissions
2008	Thomas Barker, Georgia Institute of Technology, Extracellular matrix stiffness associated with pulmonary fibrosis sensitizes alveolar epithelial cells
2008	Jiu-Chiuan Chen, University of Southern California, Particulate air pollutants, risk of cognitive disorders, and neuropathology in the elderly
2010	Jun Wu, University of California–Irvine, Adverse reproductive health outcomes and exposures to gaseous and particulate matter air pollution in pregnant women
2011	Juana Maria Delgado-Saborit, University of Birmingham, UK, Use of real-time sensors to assess misclassification and to identify main sources contributing to peak and chronic exposures
2011	Richard Peltier, University of Massachusetts, Amherst, Development of a new method for measurements of reactive oxygen species associated with $PM_{2.5}$ exposure
2012	Jason Surratt, University of North Carolina–Chapel Hill, Understanding the health effects of isoprene-derived particulate matter enhanced by anthropogenic pollutants
2013	Nga Lee (Sally) Ng, Georgia Institute of Technology, Composition and oxidative properties of particulate matter mixtures: Effects of particle phase state, acidity, and transition metals

RFA 14-4: APPLICATION PROCESS AND DEADLINES

ELIGIBILITY REQUIREMENTS

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

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

LETTER OF INTENT

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

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

Deadline for Letter of Intent: A Letter of Intent should be submitted by email to *funding@healtheffects.org* (subject line: RFA 14-2 Letter of Intent) no later than **MARCH 2, 2015**. HEI will acknowledge receipt of the letter.

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

FULL APPLICATION

Deadline for Applications: Applications for RFA 14-2 should be submitted to *funding@healtheffects.org* (subject line: RFA 14-2 Full Application) no later than **APRIL 6, 2015.** Applications should be in *PDF format* with a maximum file size of 20 MB.

After submission, please notify HEI's Science Administration Assistant (+1-617-488-2345) of your submission; do not attach the PDF documents to this second email. HEI will acknowledge receipt of the application.

Applications not meeting these conditions will not be considered.

The research proposal must be submitted on the forms **F-1 to F-12** (see list on page 37) that can be found on our website at *www.healtheffects.org/funding.htm*. Note that there is a separate set of forms for this Award; Form F-12 is optional. Investigators should consult the *Instructions for Completing the Application* found on pages 31-36. Please note that the required font size is **11 point with 1-inch margins**. Please check our website for updates. Letters of recommendation can be included with the application or be submitted to HEI directly by the referent. Please notify Dr. Sunshine which referents will be sending letters directly to HEI.

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

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

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

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

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

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

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

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

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

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

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

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

RFA 14-4: EVALUATION PROCESS

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

EXTERNAL REVIEW

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

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

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

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

INTERNAL REVIEW

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

POLICY ON FOLLOW-ON APPLICATIONS

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

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

PROCESS AND TIMING FOR SUBMISSION

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

PRELIMINARY APPLICATION

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

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

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

The preliminary application should be submitted electronically to the HEI 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 this RFA booklet, including a budget, a project plan, and any additional submissions and should be prepared using forms F-1 to F-12 (see list on page 37) that can be found on our

website at *www.healtheffects.org/funding.htm*. In the project plan, investigators should provide a brief summary of results available to date and describe the relationship between these results and the future experiments described in the proposal. Furthermore, the application should include a discussion of how anticipated results might apply to specific issues of potential health risks from exposure to air pollution.

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

CRITERIA FOR EVALUATION

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

HEI PROJECT NEGOTIATION, MANAGEMENT, AND INVESTIGATOR COMMITMENTS

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

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

SCIENTIFIC NEGOTIATION OF PROJECT PLANS

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

RESEARCH AGREEMENT (CONTRACT)

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

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

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

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

STUDIES INVOLVING HUMAN PARTICIPANTS

As mentioned in the section *Instructions for Completing the Application, Additional Submissions*, the applicant must submit, with the application, a written assurance for compliance with the guidelines established by the Environmental Protection Agency (EPA) — as specified in EPA Regulation 40 CFR 26 (Protection of Human Subjects) available from EPA's Program in Human Research Ethics (*http://www.epa.gov/osa/phre/index.htm*) — and the guidelines by the Department of Health and Human Services (DHSS) concerning protection of human participants (see pages 34-35), on OMB form No. 0990-0263 (page F-11 of HEI application forms).

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

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

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

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

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

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

QUALITY ASSURANCE AND QUALITY CONTROL

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

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

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

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

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

PROGRESS REPORTS

Progress reports are one of the ways by which HEI keeps informed of the progress of the studies that it supports. Investigators are required to submit progress reports at five and ten months of the first year of the study. In subsequent years, five- and ten-month reports are requested as well. In the final year of the contract, the ten-month progress report is replaced by a comprehensive final report (pages 27-28).

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

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

SITE VISITS

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

HEI ANNUAL CONFERENCE AND OTHER MEETINGS

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

FINAL REPORT

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

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

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

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

Investigators should be prepared to submit, upon request from HEI, information underlying the final data analyses included in the report. Such information may include data sets that contain individual data as well as statistical code and output of statistical analyses with appropriate documentation. This information will be used internally at HEI and will be made available to the Review Committee to assist in their evaluation of the final report. Selected information may be included as appendices to the final report, in consultation with the investigator. Please note that this request is separate from the *Quality Assurance and Quality Control* requirements listed on pages 26-27.

POLICY ON DATA ACCESS

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

PUBLICATIONS

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

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

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

GENERAL INFORMATION

Applications must be submitted on the *HEI Application for Research Agreement* (forms F-1 to F-12; see list on page 37). Applications should be typed single-spaced, within the margin limitations indicated on the forms (1 inch minimum), and using a minimum font size of 11 pt. Interactive forms can be downloaded from our website at *www.healtheffects.org/funding.htm*.

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

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

BUDGET (FORMS F-4 AND F-5)

Cost or Pricing Data: Provide adequate data and analysis to assure HEI that the proposed costs are necessary and reasonable and that adequate accounting procedures will be used. HEI has no specific limitation on the budgets of research proposals (with the exception of the Walter A. Rosenblith New Investigator Award). Most studies funded to date have been within a range of $125,000 to $300,000 per year, including indirect costs. Projects requiring larger budgets or time periods longer than three years must have exceptional promise of developing important methods or information for understanding the health effects of automotive emissions. For applications responding to RFA 14-3, the budget should be prepared assuming a project start date of February 1, 2016; for RFA 14-4 it should be November 1, 2015.

The total budget should include funds and an appropriate percent effort from key personnel for writing the final report in the final year of the study. Investigators should also be aware that additional time effort is expected at a later time to address requests for revisions and answering editorial queries. Please refer to the *Final Report* section on pages 27-28 for details.

PERSONNEL

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

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

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

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

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

expertise in this area, evidence of which should be submitted as part of the application. The statistician's involvement should be evident in the application, for example by including a letter from the statistician indicating that they have read the application and approve the study design and statistical approaches. (See also *Additional Submissions* on pages 34-36).

CONSULTANT COSTS

Consultant service should be explained by indicating the specific area in which such service is to be used. Identify the contemplated consultants. State the number of days of such services estimated to be required and the consultant's quoted rate per day, and indicate the number of hours per day in which work will be performed. The maximum consultant rate is $600/8-hr day. HEI's participation in consultant costs is subject to limits set by federal regulations. (See also *Additional Submissions* on pages 34-36).

SUPPLIES AND OTHER EXPENSES

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

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

TRAVEL EXPENSES

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

INDIRECT COSTS

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

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

EQUIPMENT

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

SUBCONTRACTS

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

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

OTHER SUPPORT (FORM F-6)

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

RESOURCES AND ENVIRONMENT (FORM F-7)

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

BIOGRAPHICAL SKETCHES (FORM F-8)

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

PROJECT PLAN (FORM F-9)

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

A. Objectives

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

B. Anticipated Results and Significance

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

C. Related Previous Studies

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

D. Experimental Plan and Methods

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

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

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

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

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

Where appropriate, describe the procedures to be used to ensure that the quality of the data is adequate in view of the objectives of the study (see *Quality Assurance and Quality Control* on pages 26-27). However, detailed QA information should not be submitted with the original application but will be requested for successfully funded studies that meet the above criteria.

E. Statistical Design and Analysis Plans

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

F. Literature Cited

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

ADDITIONAL SUBMISSIONS (FORM F-10)

Human Participants

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

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

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

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

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

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

If HEI decides to fund a study involving human participants, the investigator will be asked to submit a detailed protocol before starting the study and to comply with HEI's special QA/QC procedures (see *HEI Project Negotiation, Project Management, and Investigator Commitment,* and *Appendix C*). Approval of the study by the Institutional Review Board (IRB) at the investigator's institution is required before starting a study with human participants. In addition, HEI will need to obtain approval from EPA before signing the contract, as described under *HEI Project Negotiation, Project Management, and Investigator Commitment* on pages 25-29. Documentation submitted to HEI should include (1) the complete application to the IRB; (2) consent forms, if applicable; and (3) a signed letter from the IRB indicating that the study has been approved or exempted.

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

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

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

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

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

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

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

certain designated animal studies. Those studies will undergo an external audit, and the final report will include a QA Statement from the auditor(s). See *Quality Assurance and Quality Control* on pages 26-27 and *Appendix C* for more details.

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

LIST OF APPLICATION FORMS

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

Preliminary Application Form

Full Application package:

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

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

APPENDIX A: SECTIONS OF THE HEI STRATEGIC PLAN (2015–2020)

The HEI Strategic Plan 2015–2020 is currently under development. It describes the projected research programs and review activities for the period 2015–2020. This plan is being developed with ideas and input from HEI's sponsors, the scientific community and other constituents. A first draft was circulated in April 2014; a revised draft was circulated in October 2014 and is available on the HEI web site at *www.healtheffects.org*. Below, we provide an overview of the research opportunities that are included in the revised draft, which can be downloaded here: *http://www.healtheffects.org/Pubs/StrategicPlan2015-2020-RevisedDraftOctober2014.pdf* . The final Plan will be issued in April 2015.

PRIORITY RESEARCH OPPORTUNITIES 2015–2020

Based on the progress HEI has made to date, the challenges for policy and science ahead, and the comments HEI has already received on future directions from its sponsors in government and industry and the scientific community, we have identified above four major areas of significant research opportunities for consideration in HEI Strategic Plan 2015 – 2020. For each of these important areas we describe below major initiatives that HEI has underway (and will complete in the coming years), and plans to initiate to address the key challenges we have identified. In addition, as mentioned before, HEI should be flexible to take on additional research questions as they arise.

ADDRESSING CHALLENGES OF MULTI-POLLUTANT SCIENCE

During the last Strategic Plan (2010 – 2015), HEI put emphasis on new approaches to understanding multipollutant exposures and health effects. Under this broad area, HEI has now completed several major studies, including those focused on a better understanding of PM components toxicity (NPACT), improved statistical methods, air pollution from traffic, and other areas.

Many challenges to a robust understanding of these problems continue, while other research needs have also become apparent. The consideration of these challenges calls for a new level of rigorous research to answer major uncertainties. During the next five years, HEI proposes to focus its research in two broad areas:

- Estimating the effects of exposures to low levels of air pollution
  - Multipollutant studies in large populations to estimate the effects of exposure at low concentrations
  - Effects of low levels of ozone on the cardiovascular system – completion and publication of an ongoing study
- Understanding emissions, exposures, and health effects of the air pollution mixture, specifically
  - Enhanced analyses within the NPACT and ESCAPE cohorts
  - Examining exposures and health effects from traffic and port source mixtures
  - Special aspects of exposure to traffic-related source mixtures
  - The changing nature of diesel source emissions and effects

In planning and conducting new research on these topics, HEI will also enhance its efforts to have the resources and the ability to catalogue the underlying data and ultimately make them available to other investigators once the studies have been published.

HEALTH OUTCOMES AND TRANSPARENCY

Health Outcomes (Accountability)

HEI's interest and commitment to health outcomes studies stems in large measure from the importance of assessing whether potentially costly and complex regulations and other interventions are yielding the demonstrable improvements in air quality and public health that were initially projected. Early during the next Strategic Plan, HEI will complete the four studies from RFA 11-1 that are currently underway (on evaluating children's health and regulations in southern California; goods movement regulations in California; air quality regulations in the Southeastern U. S.; and statistical methods to better assess large national databases). These studies provide some of the first attempts to evaluate large scale regulations; however, there are many continuing challenges, e.g. accounting for concurrent changes in a range of environmental, health, individual and socio-economic variables.

As the second wave studies reach completion and review during the early part of the next Strategic Plan, HEI is planning to gather a small groups of experts, including HEI committee members and interested stakeholders, (similar to what was done after completion of the first wave of studies in a 2009 workshop) to review progress and chart next steps. Based on

discussions during this second workshop, the HEI Research Committee will plan the next phase of HEI's accountability program. Some of the areas likely to receive attention include:

- Studies that are more closely linked to implementation of new regulations, for example:
  - Implementation of revisions to National Ambient Air Quality Standards (e.g. $PM_{2.5}$ and Ozone),
  - Major stationary source rules addressing air quality and climate issues, including those addressing emissions from coal-fired utility and industrial sources,
  - Implementation of actions to accelerate diesel technology replacement (e.g. expenditures under the Diesel Emissions Reductions Act),
  - The effects of systematic introduction of alternative fuels over time.
- Measures specifically aimed at reducing exposure of at-risk populations.
- Smaller scale interventions aimed at improving air quality and reducing GHG emissions at the local level, e.g. interventions for improved residential efficiency (and resulting changes to ventilation) or fuel switching from diesel to natural gas.
- The development of new methods, including enhanced statistics, application of causal models, and potential use of new biomarkers of exposure or early disease included in national scale databases.

Improving Data Access

Throughout its history, HEI has had a commitment to transparency and data access, even while protecting study participant confidentiality. In addition to maintaining a strong policy on facilitating access to underlying data and methods for the studies it funds, HEI has responded to requests from government, industry, and others to reanalyze studies central to the regulatory process and evaluate their overall strengths and weaknesses, and in other cases, their suitability for use in quantitate risk assessment. Recently, interest in ownership, access and control of data underpinning scientific research has increased in Congress and the scientific and stakeholder communities and requests for HEI involvement have increased. HEI sees activities in this area as an important feature of this Plan.

During the next Strategic Plan, HEI plans to conduct one or more workshops at the science-policy interface to identify and promote approaches to data sharing, including identifying opportunities to make data more widely available, along with identification of challenges to data sharing in the context of confidentiality and other privacy protections. The workshop(s) will also focus on exploring solutions to how scientific data may be shared, an area in which HEI has had some experience.

HEI's commitment also extends to making data from HEI-funded studies available for reanalysis, verification, and extended analyses by others. Given widespread interest in both the science and policy communities in this issue, HEI will enhance its ongoing efforts to make all data underlying the studies it funds available following publication, and to build on its expertise in this area.

EMERGING FUELS AND TECHNOLOGIES

HEI has long provided critical information on key emerging questions relevant to vehicles and fuels, including emerging diesel technologies, alcohol fuels, and manganese and MBTE as fuel additives. More recently, HEI undertook a major initiative – the Advanced Collaborative Emissions Study (ACES) – to characterize emissions from new technology 2007 and 2010 heavy duty diesel engines and assess the health effects of emissions from a 2007 engine in laboratory animals. Additionally, through the Special Committee on Emerging Technologies (SCET), HEI has established a mechanism to obtain and provide an ongoing understanding of emerging new technologies and fuels.

In view of concerns about not only air pollution but also climate change and energy security, there is a need to find new solutions to enable mobility for the public, while overcoming problems related to climate, energy security, and cost, along with air pollution. Recent regulatory activities in Europe, the United States, the State of California and many other parts of the world have been specifically focused on combating various aspects of this set of challenges. This situation also provides the impetus for development and introduction of a broad range of new fuels, technologies, and sources of energy to meet the needs of the transportation sector. Over the next five years, concerns that may arise from the use of new fuels and technologies will remain a priority for HEI research.

GLOBAL HEALTH SCIENCE

With supplemental support, HEI has worked carefully for many years to extend its work in the US both in Europe, where science is often directly relevant to the US, and in the developed world, to provide credible, policy relevant science and capacity building to inform decisions in the developing nations of Asia and Latin America. HEI's ability to attract support for such studies greatly leverages the initial investment of EPA and industry to obtain new science relevant not only in the

developing world, but to take advantage of unique research opportunities found there to provide science relevant to decisions in the US and Europe as well.

Science to understand air pollution health effects is much needed in China, India, and developing Asia, where air pollution from a broad range of sources directly impacts the health of local populations, is transported to Japan and the Western US (impacting the health of populations there), and contributes a large percentage of global GHG emissions. Indeed, the 2010 Global Burden of Disease (GBD) found that ambient air pollution was associated with over 3.2 million premature deaths worldwide of which fully two-third are in developing Asia.

It is in the interest of regulators and the regulated community alike to support high quality science, capacity building, and active communication to policy makers to engage and equip developing nations to understand and respond to the health, economic, and environmental benefits associated with pollution reduction for local and global benefit. HEI has attracted significant additional support for its international work in the past, including from the European Union and industry to work in partnership with WHO on Air Quality Guidelines, and from domestic and international foundations for science at the global level.

During the 2015-2020 Plan, HEI plans to implement a strong global program through a range of initiatives, including:

- Supporting broadly relevant science in Europe: enhanced analyses within the NPACT and ESCAPE cohorts
- Global Burden of Disease
- Targeted new research in Asia
- Capacity building
- Active communication to policy makers

CROSS-CUTTING ISSUES

In reviewing the detailed major opportunities for new research that HEI proposes to address going forward, a number of other questions were identified that would not by themselves be programs of research in the new Strategic Plan, but we view these as cross-cutting issues that should be integrated into all of HEI's work.

- Development, application, and testing of multi-pollutant statistical models and methods
- At risk populations
- Enhanced exposure assessment
- Climate change and health
- Application of new biological techniques in air pollution health research
- Other health outcomes and modifying factors
- Capacity building: support of early-career investigators

APPENDIX B: HEI STUDIES AND RESEARCH REPORTS FROM 2004-2014

RFA 14-2: WALTER A. ROSENBLITH NEW INVESTIGATOR AWARD
Study under negotiation

RFPA 14-1: ENHANCING NEAR-ROAD EXPOSURE ASSESSMENT THROUGH CHARACTERIZATION OF NON-TAILPIPE AND TAILPIPE EMISSIONS NEAR URBAN ROADS AND IN TUNNELS
Petros Koutrakis, Harvard School of Public Health
Chemical and physical characterization of non-tailpipe and tailpipe emissions at 100 locations near major roads in the greater Boston area (Study under negotiation)
Xiaoliang Wang, Desert Research Institute
Real-world vehicle emission characterization for the Shing Mun tunnel in Hong Kong and the Ft. McHenry Tunnel in the US (2016)

RFA 13-2: WALTER A. ROSENBLITH NEW INVESTIGATOR AWARD
Sally Ng, Georgia Institute of Technology
Composition and oxidative properties of particulate matter mixtures: effects of particle phase state, acidity, and transition metals (2017)

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

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

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

RFPA 10-3:
Alison Fryer, Oregon Health and Science University
Air pollution and systemic inflammation of autonomic nerves. (2015)

David Rich, University of Rochester and **Annette Peters,** Helmholtz Center Munich, Germany
Ambient and controlled particle exposures as triggers for acute ECG changes, and the role of antioxidant status. (Completed)
William Kraus, Duke University
Air quality by genomics interactions in a cardiovascular disease cohort (2017)

RFA 10-2: WALTER A. ROSENBLITH NEW INVESTIGATOR AWARD
Juana Maria Delgado-Saborit, University of Birmingham, UK
Use of real-time sensors to assess misclassification and to identify main sources contributing to peak and chronic exposures. (2016)
Richard Peltier, University of Massachusetts, Amherst
Development of a new method for measurements of reactive oxygen species associated with $PM_{2.5}$ exposure. (2015)

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

RFPA 09-5: HEALTH EFFECTS OF AIR POLLUTION
Gunnar Boysen, University of Arkansas
Profiling doses of reactive compounds derived from various air pollutant exposures. (Unpublished Report)
Myoseon Jang, University of Florida
Pilot study: A Novel Exposure Method to Evaluate the Health Effects of Combustion Particulate Matter. (Unpublished Report)
Fern Tablin, University of California
Immune effects of episodic ozone and PM exposure during postnatal development. (Unpublished Report)

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

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

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

RFA 09-1: METHODS TO INVESTIGATE THE EFFECTS OF MULTIPLE AIR POLLUTION CONSTITUENTS
Brent Coull, Harvard School of Public Health
Statistical learning methods for the effects of multiple air pollution constituents. (Completed)
John Molitor, Oregon State University
Modeling of multi-pollutant profiles with applications of RIOPA study data and to indicators of adverse birth outcomes using data from the UCLA Environment and Pregnancy Outcome Study (EPOS). (2014)

Eug-Sun Park, Texas A & M University
Development of enhanced statistical methods for assessing health effects associated with an unknown number of major sources of multiple air pollutants. (Completed)

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

RFA 08-1: RELATIONSHIP OF INDOOR, OUTDOOR AND PERSONAL AIR (RIOPA): FURTHER ANALYSES OF THE RIOPA STUDY DATA
Stuart Batterman, University of Michigan
Relationship of indoor, outdoor and personal air (RIOPA): Further analyses of the RIOPA study data. (Report No. 181)
Patrick Ryan, University of Cincinnati
Analysis of personal and home characteristics associated with the elemental composition of $PM_{2.5}$ in indoor, outdoor and personal air in the RIOPA study. (Completed)

RFA 07-1: WALTER A. ROSENBLITH NEW INVESTIGATOR AWARD
Thomas Barker, Georgia Institute of Technology
Extracellular matrix stiffness associated with pulmonary fibrosis sensitizes alveolar epithelial cells. (Report No. 182)
Jiu-Chiuan Chen, University of Southern California
Particulate air pollutants, risk of cognitive disorders, and neuropathology in the elderly. (2014)

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

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

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

RFA 06-3: WALTER A. ROSENBLITH NEW INVESTIGATOR AWARD
Charles Stanier, University of Iowa
Development and application of a personal exposure screening model for size-resolved urban aerosols. (Report No. 179)
Yifang Zhu, Texas A&M University
Assessing children's exposure to ultrafine particles from vehicular emissions. (Report No. 180)

RFA 06-2: ADDITIONAL HEALTH EFFECTS ENDPOINTS DURING THE CHRONIC BIOASSAY
Jeffrey Bemis, Litron Laboratories
Genotoxicity of inhaled diesel exhaust: examination of rodent blood for micronucleus formation. (Report No. 166, Part 2; Report No. 184, Part 2)
Daniel Conklin, University of Louisville
Effects of diesel emissions on vascular inflammation and thrombosis. (Report No. 166, Part 4; Report No. 184, Part 4)
Lance Hallberg, University of Texas Medical Branch
Assessment of the genotoxicity of diesel exhaust from improved diesel engines. (Report No. 166, Part 3; Report No. 184, Part 3)

Qinghua Sun, Ohio State University
Diesel exhaust exposure and cardiovascular dysfunction: ROS mechanism. (Study terminated)
John Veranth, University of Utah
Lung cell gene transcription responses to diesel exhaust. (Study terminated)

RFP 06-1: EXPOSURE FACILITY AND CONDUCT OF A CHRONIC INHALATION BIOASSAY
Joe Mauderly and Jacob McDonald, Lovelace Respiratory Research Institute
Development of a diesel exhaust exposure facility and conduct of a chronic inhalation bioassay in rats and 90-day study in mice. (Phase 3A: Communication 17; Phase 3B: Report No. 166, Part 1; Report No. 184, Part 1)

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
Effects of Short-Term Exposure to Air Pollution on Hospital Admissions of Young Children for Acute Lower Respiratory Infections in Ho Chi Minh City, Vietnam. (Report No. 169)
HEI Collaborative Working Group on Air Pollution, Poverty, and Public Health in Ho Chi Minh City
The relationship between personal and ambient exposures in Ho Chi Minh City. (Completed)

RFPA 05-3: HEALTH EFFECTS OF AIR POLLUTION
Robert Brook, University of Michigan
Pilot Study: Effect of ambient fine particulate matter exposure on coronary vascular function and myocardial perfusion. (Unpublished Report)
Eric Jordt, Yale University
Pilot study: TRPA1 channels in airway sensory nerve ending as mediators of the irritant effects of acrolein. (Unpublished Report)
Debra Laskin, Rutgers University
Role of TNF-alpha in diesel exhaust-induced pulmonary injury in elderly mice. (Report No. 151)
Qinghua Sun, Ohio State University
Pilot Study: Diesel exhaust particle effects on angiogenesis. (Unpublished Report)
Junfeng Zhang, University of Medicine and Dentistry of New Jersey
Molecular and physiological responses to drastic changes in PM concentration and composition. (Report No. 174)

RFA 05-2: WALTER A. ROSENBLITH NEW INVESTIGATOR AWARD
Christopher Paciorek, Harvard School of Public Health
Integrating monitoring and satellite data to retrospectively estimate monthly $PM_{2.5}$ concentrations in the eastern United States. (Report No. 167)
Qunwei Zhang, University of Louisville
Activation of endothelial cells and gene expression in lungs following exposure to ultrafine particles. (Unpublished Report)

RFA 05-1B: CONDUCTING PLANNING OR DEMONSTRATION STUDIES TO DESIGN A MAJOR STUDY TO COMPARE CHARACTERISTICS OF PARTICULATE MATTER ASSOCIATED WITH HEALTH EFFECTS
JoAnn Lighty, University of Utah
A planning study to investigate the impacts of dust and vehicle-related PM on acute cardiorespiratory responses in the arid Southwest. (Unpublished Report)

RFA 05-1A: CONDUCTING FULL STUDIES TO COMPARE CHARACTERISTICS OF PM ASSOCIATED WITH HEALTH EFFECTS
Morton Lippmann, New York University
Characteristics of PM associated with health effects. (Report No. 177)
Sverre Vedal, University of Washington
Integrated epidemiologic and toxicologic cardiovascular studies to identify toxic components and sources of fine PM. (Report No. 178)

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

Johannes Filser, GSF-Forschungszentrum für Umwelt und Gesundheit
Pilot study: Quantification of oxidative stress resulting from ambient air; contribution of specified compounds. (Unpublished Report)
Ian Kennedy, University of California, Davis
The uptake of ultrafine particles by vascular endothelial cells and inflammation. (Report No. 136)
Robert Lux, University of Utah
Air pollution effects on ventricular repolarization. (Report No. 141)
John Repine, University of Colorado
Pilot Study: Toxicity of inhaled carbonaceous particles generated under low air-fuel combustion ratio. (Unpublished Report)
Isabel Romieu, Instituto Nacional de Salud Pública
Multi-city study of air pollution and health effects in Latin America. (Report No. 171)
Holger Schulz, GSF-Forschungszentrum für Umwelt und Gesundheit
Pilot study: Systemic effects of inhaled ultrafine particles on the progress of inflammatory and cardiovascular disease. (Unpublished Report)
Simon Wong, University of Arizona
Pilot study: The molecular effects of diesel exhaust particulates on respiratory neutral endopeptidase. (Unpublished Report)

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

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

RFPA 04-3: HEALTH EFFECTS OF AIR POLLUTION
Michael Oldham, University of California at Irvine
Pilot study: Dosimetry in compromised animal models of human disease. (Unpublished Report)
Maria Morandi (Marek Radomski), University of Texas
Pilot study: Mechanisms of PM-associated exacerbation of endothelial dysfunction. (Study terminated)
James Robins, Harvard School of Public Health
New statistical approaches to semiparametric regression with application to air pollution research. (Report No. 175)

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

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

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

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

PART 1. GENERAL QUALITY ASSURANCE / QUALITY CONTROL PROCEDURES

1.1. POLICY STATEMENT

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

1.2. QUALITY ASSURANCE / QUALITY CONTROL COMPONENTS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1.3. ROLES OF INSTITUTIONS AND INDIVIDUALS IN ACHIEVING QUALITY ASSURANCE

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

The QA plan shall include:

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

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

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

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

PART 2. SPECIAL QA/QC PROCEDURES

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

2.1 THIRD-PARTY QA OVERSIGHT

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

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

2.2. ELEMENTS OF A QA AUDIT

The key elements of a QA audit include:

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

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

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

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

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

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

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

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

2.3. TIMING OF QA AUDIT

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

A. Audits during the course of the research period

1. Clinical studies

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

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

2. Epidemiologic, statistical, and other studies

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

B. Audit of the final report

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

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

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

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

This policy applies to all research funded by HEI; it is consistent with amendments to Office of Management and Budget (OMB) Circular A-110 which requires 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. *Research Data* The research data that will be made available in response to requests 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 replicate and verify the original research findings. It will include digital records including analytical summary and computer codes, where appropriate, but 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) personal and medical information and similar information that is personally identifiable, and 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.
2. *Data Plan and Provision of Access to Research Data* HEI will expect each Principal Investigator (PI) it funds to provide, at the outset of the study: (1) a plan for organizing, protecting, archiving and making all data, data descriptions, analytical summary and computer codes described above available to HEI upon completion of the study, and (2) a plan for making research data available to other investigators following publication of the results as set forth under this policy. In 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 PI might as an alternative 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.
3. *Third Party Data* In cases where the PI uses data for HEI sponsored research collected by a third party – whether public or private – and the PI is contractually bound with the third party to keep the data confidential, HEI and/or the PI will provide information on the process the third party has in place for access to the data and will direct the requestor to the third party to seek access to the data; wherever possible, HEI will facilitate this process. HEI will provide access to third party data only when such access is consistent with the confidentiality or other obligations HEI or its PIs have with respect to such data.
4. *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 PI 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 PI interests against the need for interested parties to obtain access in a timely manner.
5. *Length of Data Retention* HEI funded PI are required to retain all data generated in the course of HEI-funded research for at least ten (10) years from the date of publication of the research by HEI, or a longer period if required by a funding agency or third party data provider or as directed by HEI. HEI retains the right to access the data at any time during this period. If the PI has kept the data beyond this time, HEI will continue to have the rights to access to the data. At any point, and at least ninety (90) days prior to any alteration or destruction or

other disposal of the data, the PI will notify HEI so as to enable the Institute to request such data under this provision.

6. *Responsibility and Reimbursement for Costs* To the maximum extent possible, HEI will encourage the PI to be the primary sharer of the data. To the extent that providing the data would place an undue burden on the PI (e.g. in a situation where the sheer number of requests would not allow the PI to continue to conduct her or his research or academic activities), 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 requester's reasonable reimbursement for both the direct costs of providing the data, and for the time of the PI 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 PI expect that the results have a high likelihood of being used in supporting a regulatory decision, HEI will consider requests from the PI for a reasonable budget of data archiving funds, to be provided as part of the project budget.
7. *Confidentiality* Any requester of research data will be expected to obtain any approvals and enter into any required data use agreements necessary to permit the requester access to such data. The requestor will be fully responsible for adhering to all such approvals from the appropriate agencies (e.g. the National Center for Health Statistics) or other third party data providers. HEI will not knowingly itself provide, or require a PI to provide, information that can be used to identify a specific individual without the requester having already obtained all such necessary approvals.
8. *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 PI and HEI promptly of any findings emerging from their analysis, to provide the PI an opportunity to respond to those findings prior to publication, to provide copies to both the PI and HEI of any papers submitted for publication from the data, and to cite both HEI and the PI in any publication, noting explicitly that the views expressed are those of the new analyst and not those of the PI , HEI, or HEI's sponsors.
9. *HEI Decision Making* All requests for research 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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