



## REQUEST FOR APPLICATIONS 20-1A: HEALTH EFFECTS OF AIR POLLUTION

### INTRODUCTION

This Request for Applications (RFA) provides a mechanism for investigators whose area of interest falls outside of current RFAs, but is compatible with the HEI research program and mission, to apply for HEI funds. HEI is interested in receiving applications for research on novel and important aspects of the health effects of air pollutants. Applicants will be asked to submit a preliminary application. Full applications will be by invitation only. HEI is particularly interested in applications that address the following topics:

- (a) Accountability or effectiveness of air quality interventions
- (b) Strengthening causal interpretation of evidence from existing cohorts
- (c) Contribution of wildland and agricultural burning to air quality and health

Additionally, applications will be considered not only on these three specific topics, but also on other issues related to improving our understanding and assessment of the health risks of exposure to motor vehicle emissions, secondary pollutants derived from them, and the whole air pollution mixture to which they contribute. HEI's current areas of interest are described in the draft [HEI Strategic Plan for the Health Effects of Air Pollution 2020-2025](#). More detailed information on the three specific topics is provided below.

This RFA has been updated to reflect a new schedule related to the coronavirus pandemic. HEI has added RFA 20-1B to study the link between air pollution, SARS-CoV-2, and public health. Please see RFA 20-1B for details.

### STUDY DURATION AND BUDGET GUIDELINES FOR RFA 20-1A

HEI encourages interested applicants to submit preliminary applications for projects of varying lengths and budgets as follows:

- (1) Small to medium-sized studies of 2 years in duration with a maximum budget of \$500,000, to pursue a specific research question that can be completed in the specified time frame.
- (2) Medium to large-sized studies of up to 3 years in duration with a maximum budget of \$800,000, to pursue a more complex research project with multiple related specific aims.

Preparation of the final report should be included in the budget and timeline of the final year of the study. Total available funding is \$2 million; HEI expects to fund three to five studies from RFA 20-1A.

### THE HEI RESEARCH PROGRAM AND RESEARCH PRIORITIES

Since the early 1980s, HEI's research has addressed a broad range of questions about the health effects of air pollutants derived from motor vehicles emissions, including, carbon monoxide, nitrogen oxides, ozone, particulate matter (PM) — including diesel particles and associated compounds — methanol, and air toxics. Several studies have addressed the effects of exposure to more than one pollutant. In considering potential research topics outside of the three identified in this RFA, applicants should be aware of HEI's current areas of interest, as described in the draft HEI Strategic Plan for the Health Effects of Air Pollution 2020-2025.

The new Strategic Plan focuses on four key areas: (1) Accountability: testing the links between air quality and health; (2) Questions related to the complexity of the air pollution mixture; (3)



Transportation and urban health; and (4) Global health. Appendix A<sup>1</sup> includes sections of the Strategic Plan 2020-2025 that describe HEI's current research priorities and plans for implementing them. Interested readers can refer to HEI's website for information on studies that were funded in recent years (see [www.healtheffects.org/publications](http://www.healtheffects.org/publications) under "Research Reports" for past studies as well as [www.healtheffects.org/research/ongoing-research](http://www.healtheffects.org/research/ongoing-research) for current studies).

HEI studies have used a wide range of designs: modeling, methods development, experiments with cell cultures, animal studies, controlled human exposure studies, and epidemiologic investigations. In all studies, HEI places strong emphasis on accurate characterization of exposure and appropriate statistical analyses. HEI's ultimate goal is to provide scientific evidence that can be used in regulatory decisions or provide better information for risk assessment; thus, human studies and studies to improve extrapolation from animals to humans are both important parts of HEI's program.

## **OBJECTIVES**

While we believe that an understanding of scientific questions outlined in HEI's research priorities, as described in the HEI Strategic Plan, are important, one of the goals of this RFA is to provide a means for investigators to suggest novel lines of research. Thus, applications will be considered not only on three specific topics outlined below, but also on other issues related to improving our understanding and assessment of the health risks of exposure to motor vehicle emissions, secondary pollutants derived from them, and the whole air pollution mixture to which they contribute.

### **Accountability or effectiveness of air quality regulations**

Accountability research refers to empirical studies that assess the effects of air quality actions, including regulatory actions, other interventions, or "natural" experiments on air pollution and health (sometimes also referred to as intervention studies). HEI's interests include unique opportunities to study well-documented changes in air quality resulting from regulatory or other actions in ports areas (targeting both shipping and airport emissions), low emission zones, and so-called diesel bans. HEI is also interested in studies that develop, apply, and disseminate novel statistical and other methodology for conducting accountability research.

Readers should refer to HEI's recent RFA 18-1, [Assessing Improved Air Quality and Health From National, Regional, and Local Air Quality Actions](#), for more details about desirable attributes of accountability research. Additional background information can be found in HEI Communication 11, [Assessing Health Impact of Air Quality Regulations: Concepts and Methods for Accountability Research](#) (HEI Accountability Working Group 2003), which sets out a conceptual framework for assessing the health effects of air quality actions. Some of the challenges confronted in accountability research are also discussed in commentaries of several HEI Research Reports (see [HEI Publications](#), select topic Accountability). Finally, various recent reviews have summarized findings and lessons learned from accountability research conducted to date (e.g. van Erp and Cohen 2009; Health Effects Institute 2010; Henschel et al 2012; Boogaard et al 2017; Henneman et al 2017; Rich 2017).

### **Strengthening causal interpretation of evidence from existing cohorts**

The determination of "causality" for relationships between air pollution and adverse health outcomes is important to improve scientific knowledge and inform policy. In many regulatory settings, this has been based on a "strength of evidence" approach, drawing on various lines of evidence ("triangulation") from epidemiology, animal toxicology and mechanistic human clinical studies (Dominici and Zigler 2017; Owens et al 2017; Pearce et al 2019). Discussions regarding how to establish causality of air pollution effects have re-emerged recently (Cox 2018). Randomized study

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<sup>1</sup> All information and forms referred to in this RFA are available at [www.healtheffects.org/research/funding](http://www.healtheffects.org/research/funding)

designs are widely seen as the gold standard in clinical research, because they can avoid confounding as a potential limitation of non-randomized studies. However, randomized study designs are in most cases not applicable to questions of human hazard identification and quantification, such as those that occur in long-term air pollution epidemiology. Traditionally, regression models have served as the cornerstone statistical approach in environmental epidemiology to derive inferences about health effects, estimated as relative risks or hazard ratios (Carone et al. 2019). However, information about confounders, and exposures and doses, is never perfect, leading to (unresolvable) concerns about the true nature of the association.

Evolving causal modeling approaches for the analysis of epidemiologic studies in air pollution and health attempt to overcome these challenges; examples of such approaches include the use of instrumental variables, difference in differences, and propensity scores (Bind, 2019; Wu et al. 2019, Dominici and Zigler 2017). While the field of causal inference has the potential to greatly advance air pollution epidemiology and inform related policy, it should not be seen as the “methodologic silver bullet” (Carone et al. 2019). Since no statistical approach can fully overcome the inherent challenges of making causal inferences about air pollution health effects – stemming from the observational nature of the available data as well as the difficulty in measuring exposure – at this time a “pluralistic approach” appears to be the best option (Pearce et al. 2019). Thus, novel causal inference methods are best employed alongside traditional epidemiologic methods and combined with innovative study designs. HEI is interested in studies that examine or develop various causal inference methods that address the complexities in the design of the air pollution epidemiologic studies and nature of the data, and apply them to existing cohorts or other population data sets, contrasting the results of such methods with traditional approaches, such as regression analysis.

### **Contributions of wildland and agricultural burning to air quality and health**

With changes in regulations and technologies, urban air pollution from the transportation and energy sectors in the United States has declined in the recent decades. At the same time, the frequency and intensity of wildland fires have been increasing, adding significantly to the cumulative exposures of populations in urban as well as rural areas. In addition to unintended forest and peatland fires, there is increased use of prescribed burning to prevent extreme fires, while other regions may experience agricultural burning, for example sugar cane fields in Florida. The overall contribution of uncontrolled biomass combustion on air quality and health is particularly severe in the Western United States where wildland fires are frequent and the control of certain air pollutants—for example, ozone—has been very challenging.

Wildfire smoke is recognized for its serious impact on air quality (Cascio 2018; U.S. Environmental Protection Agency, 2019). Wildfire smoke composition is complex and highly dynamic, depending on the fuel type and fire intensity, making exposure monitoring and characterization difficult. Most fires consume vegetation (forests or peatlands) but may also include man-made structures, with emissions from burning plastics and other materials. Increasing evidence links air pollution from wildfire smoke to adverse health effects, in particular respiratory morbidity (Liu et al 2015; Reid et al 2016; Black et al 2017; Balmes, 2018; Kondo et al 2019). HEI is interested in studies in North America, Western Europe, and other high-income regions (e.g., Australia) that would provide further insights into exposure and health effects associated with wildland fires and prescribed burning, and which population subgroups may be more susceptible to the effects of wildfire smoke.

### **Other topics**

Applications will be considered not only on these three specific topics, but also on other issues related to improving our understanding and assessment of the health risks of exposure to motor vehicle emissions, secondary pollutants derived from them, and the whole air pollution mixture to which they contribute. HEI’s current areas of interest are described in the draft HEI Strategic Plan for the

Health Effects of Air Pollution 2020-2025. Applicants interested in studying SARS-CoV-2 and air pollution should apply under RFA 20-1B.

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## RFA 20-1A: APPLICATION PROCESS, DEADLINES, AND EVALUATION

The application process consists of two stages. The first stage involves the submission of a preliminary application, which is reviewed by the [HEI Research Committee](#). If the Research Committee has an interest in the study, then the investigator will be invited to prepare a full application. Invited full applications will be sent out for external peer review and discussed by the Research Committee at a subsequent meeting.

### PRELIMINARY APPLICATION

Applicants should submit a brief Preliminary Application that provides the following information: title, scientific rationale, a brief description of the study aims, design and methods, statistical methods, and anticipated results. An estimated total budget and study duration should be provided, choosing from the 2 options provided. In addition, brief biosketches (maximum 2 pages per person) of the principal investigator and key co-investigator(s) should be provided.

Investigators should use the Preliminary Application Form provided on the HEI website. The preliminary application must be no more than **4 pages in length** (using 11-point font size and 1-inch margins, single-spaced; including the cover page, but excluding references and biosketches); longer applications will be rejected. Applicants can use HEI form F-8 or another format, as long as each biosketch is no longer than 2 pages. For detailed instructions please visit [www.healtheffects.org/research/funding/application-instructions](http://www.healtheffects.org/research/funding/application-instructions). The application form and CVs should be combined into a **single PDF with appropriate bookmarks** (file name: *PI-last-name-RFA-20-1A-Preliminary application.pdf*) before submitting.

### Deadline for Preliminary Applications

Preliminary applications should be submitted by e-mail in PDF format to [funding@healtheffects.org](mailto:funding@healtheffects.org) (subject line: *PI last name RFA 20-1A Preliminary application*) no later than **AUGUST 19, 2020**, with a copy to Ms. Lissa McBurney ([science-admin@healtheffects.org](mailto:science-admin@healtheffects.org)). HEI will acknowledge receipt of the application.

### Preliminary Application Evaluation Process

Preliminary applications will be reviewed by the Research Committee and based on relevance of the proposed research to HEI's mission as well as scientific merit of the preliminary application, a limited number will be invited for a full application. Applicants will be informed whether or not to submit a full application by early November. For questions contact HEI at [funding@healtheffects.org](mailto:funding@healtheffects.org) ).

### FULL APPLICATION

Full applications without pre-submission of a preliminary application and invitation from the Research Committee will not be considered. A full application will provide, in detail, the study aims, design, rationale, methods, and statistical analyses. If data from other studies are going to be used, information on the type of data available (including the period, location, and frequency of when the measurements were taken) and quality assurance should be included. Investigators should also discuss whether they will need to obtain IRB approval. A letter from the investigator who owns the data should be submitted, stating his or her willingness to share the data with the applicant and with HEI, if requested (see [HEI Policy on the Provision of Access to Data Underlying HEI-funded Studies](#)).



Investigators invited to submit a full application should use forms **F-1 to F-12** and consult the [Instructions for Completing the Application](#). Please note that the required font size is **11 point with 1-inch margins**. The application forms should be combined into a single PDF (filename *PI-last-name-RFA-20-1A-Full-application.pdf*) with appropriate bookmarks before submitting. For details and forms please visit [www.healtheffects.org/research/funding](http://www.healtheffects.org/research/funding). Applicants should familiarize themselves with HEI's study oversight and review procedures, which are more involving than a typical NIH grant, see [www.healtheffects.org/research/investigators/commitments](http://www.healtheffects.org/research/investigators/commitments).

### **Deadline for Full Applications**

Invited Full Applications for RFA 20-1A should be submitted to [funding@healtheffects.org](mailto:funding@healtheffects.org) (subject line: *PI last name RFA 20-1A Full application*) no later than **JANUARY 6, 2021**. The application should be in PDF format with a maximum file size of 20 MB.

After submission, please notify Ms. Lissa McBurney ([science-admin@healtheffects.org](mailto:science-admin@healtheffects.org)) of your submission; do not attach the PDF documents to this email. HEI will acknowledge receipt of the application. Applicants will be notified about the funding decision by March, 2021.

### **Full Application Evaluation Process**

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

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

Second, the Research Committee will evaluate the full applications with consideration of the reviewers' comments and of the ways the proposed research might improve the understanding of the specific problem under investigation. The Research Committee's recommendation about funding will also consider whether studies are relevant to HEI's Strategic Plan and how they would complement HEI's ongoing research program, keeping in mind available resources. The Research Committee makes final recommendations regarding funding of studies to the Institute's Board of Directors, which makes the final funding decision. Note that HEI's review process is single-blinded, i.e. the identity of external reviewers and Committee members providing specific comments is not revealed to the applicants.

### **CONFLICTS OF INTEREST**

HEI's procedures for conflicts of interest are similar to the guidelines set forth by NIH. Members of HEI's sponsor community are excluded from participating in RFA development, applying for support, application review, and funding decisions. Members of HEI's Research Committee who are expected to be interested in applying were excluded from developing the RFA (or in this particular case, excluded from developing particular sections).

HEI invites external reviewers (or in the case of a major RFA, Review Panel members) who are unlikely to have a conflict of interest with the proposal(s) they are asked to review. A conflict occurs when the reviewer is named on the application in a major professional role; the reviewer (or close

family member) would receive a direct financial benefit if the application is funded; the PI or others on the application with a major role are from the reviewer's institution or institutional component (e.g., department); during the past three years the reviewer has been a collaborator or has had other professional relationships (e.g., served as a mentor) with any person on the application who has a major role; the application includes a letter of support or reference letter from the reviewer; or the reviewer is identified as having an advisory role for the project under review. In addition, HEI Staff screen external reviewers for potential conflicts of interest with other applicants who have submitted a proposal under the same RFA.

HEI discourages members of the Research Committee to apply to its RFAs, to avoid the appearance of a conflict of interest. However, in some situations it may not be possible to avoid all possible conflicts of interest as outlined above. In such cases, Review Panel and Research Committee members who have a conflict of interest will not be assigned to review the application(s) in question and will be asked to leave the room during the discussion of those application(s). They will also not score or vote on the application(s) at issue and refrain from commenting on them during the overall discussion, and in the case of the Research Committee, from all deliberations regarding recommendation of applications for funding. If several Research Committee members are recused from the overall discussion of applications for such reasons, HEI will invite external consultants to join the Committee to fill in the missing expertise.

This peer review system relies on the professionalism of each reviewer, Review Panel member, and Research Committee member to declare to HEI the existence of any real or apparent conflict of interest. If a reviewer feels unable to provide objective advice for any other reason, he/she is expected to recuse him/herself from the review of the application(s) at issue.

*This document was issued by HEI in January 2020; a revised version was posted in May 2020.*

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