



## **REQUEST FOR APPLICATIONS 20-1B: AIR POLLUTION, COVID-19, AND HUMAN HEALTH**

### **INTRODUCTION**

This Request for Applications (RFA), solicits applications for research on novel and important aspects of the intersection of exposure to air pollution and COVID-19 health outcomes. Applicants will be asked to submit a detailed letter of intent, followed by an invited full application, using an expedited application review process. HEI is particularly interested in applications that address the following questions:

- (a) Accountability research: What are the effects of the unprecedented interventions taken to control the COVID-19 pandemic on emissions, air pollution, and human health?
- (b) Susceptibility factors: Are individuals/populations who have been chronically or acutely exposed to higher levels of air pollution at greater risk of mortality from COVID-19 compared to those exposed to lower levels of air pollution? Do the effects differ by race/ethnicity or by measures of socioeconomic status?

More detailed information is provided below.

### **STUDY DURATION AND BUDGET GUIDELINES FOR RFA 20-1B**

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

- (1) Small studies of 1 year in duration with a maximum total budget of \$250,000 (direct and indirect costs), to pursue a research project using existing data.
- (2) Small to medium-sized studies of 2 years maximum in duration with a maximum total budget of \$500,000 (direct and indirect costs), to pursue a specific research question that can be completed in the specified time frame.

Preparation of the final report should be included in the budget and timeline of the final year of the study. Total available funding for projects funded under RFA 20-1B is \$2 million. The number and type of studies recommended for funding will be contingent on merit as well as programmatic review and the availability of funds.

Prospective applicants are required to submit a focused Letter of Intent, which should include a synopsis of the project, indicating the specific aims, the general approach to be used, a list of all participating institutions, and an estimated budget, using the template provided. The Letter of Intent is required, but please contact HEI should timely submission of the letter of intent pose a challenge. HEI will use the Letters of Intent to help organize the application review process. If deemed necessary, HEI will contact applicants to let them know the proposed research is not responsive to the RFA, or to advise them on how to make their applications more relevant to the specific objectives of the RFA.

### **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. HEI's new [Strategic Plan for the Health Effects of Air Pollution 2020-2025](#) 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. Interested readers can refer to HEI's website for information on studies that were funded in recent years (see [HEI Publications](#) under "Research Reports" for past studies as well as [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.

## **OBJECTIVES**

This RFA responds specifically to the unique situation created by the SARS-CoV-2 virus pandemic. Closing of non-essential businesses in many locations has led to reduced emissions of air pollutants from the energy sector and other industries, as well as significantly reduced traffic volume due to stay-at-home policies. As of spring 2020, various research efforts are underway to study the intersection of air pollution and coronavirus. There are many questions that require careful evaluation, in particular because the context within which we study the linkages between air pollution and health have changed due to COVID-19 (including emission sources; changes in behavior that affect exposures (for example people spending more time indoors; health care access and utilization, etc), which may act in opposite directions; the extent to which these changes will persist is not clear. Based on its proven record of funding high quality research on air pollution and health, HEI has formulated specific research objectives where it expects to make a valuable contribution to this rapidly expanding new field of research.

### **Air Pollution, COVID-19, and Human Health Outcomes**

HEI is interested in applications for studies designed specifically to address the following questions related to COVID-19, air quality, and human health:

- 1) **Accountability Research:** What are the effects of the unprecedented interventions implemented to control the COVID-19 pandemic on emissions, air pollution exposures, and human health? Emerging evidence suggests that changes in economic activity and human mobility following government restrictions have led to noticeable reductions in pollutant emissions and pollutant concentrations in ambient air – in particular nitrogen dioxide – in many cities around the world (Ogen 2020; Schiermeier 2020; Zhang et al. 2020). Changes in PM<sub>2.5</sub> pollution have been more limited and are less consistent (Dantas et al. 2020; Sharma et al. 2020).

The observed changes in air quality present a unique opportunity for accountability research of this "natural experiment." However, the long history of accountability research (e.g., Boogaard et al 2017; Health Effects Institute 2003, 2010; Rich 2017) indicates that well-designed and rigorous analyses are critical to characterize the effects of interventions at urban, regional, and national scales on emissions from specific sources (e.g. transport, energy, and other sectors), air pollutant concentrations, and ultimately measures of human health.

The proposed studies need to consider appropriate time periods for comparison. It may be very difficult to find control populations not affected by the interventions; in addition, interventions in various locations have occurred during different time periods. Conducting such studies will be challenging to parse amidst the dynamics of the epidemic, a major reorientation of our health care systems to deal with COVID-19, and accompanying challenges in estimating comparable hospitalization rates and other health outcomes at a time when utilization of health care may also

have changed and diagnostic criteria for COVID-19 and respiratory outcomes have been variable across time and space. Studies investigating health effects need to account for these types of changes. HEI welcomes innovative and well-designed proposals to study the effects of air quality reductions due to the COVID-19 interventions on morbidity and mortality health outcomes.

- 2) **Susceptibility Factors:** Are individuals/populations who have been chronically or acutely exposed to higher levels of air pollution at greater risk of mortality from COVID-19 compared to those exposed to lower levels of air pollution? Do the potential effects differ by race/ethnicity and by measures of socioeconomic status?

Limited evidence from the 2002-2004 SARS outbreak indicates a possible association between higher air pollution concentrations and higher than expected death rates (Cui et al. 2003; Kan et al. 2005). Recent evidence suggests that individuals with existing co-morbidities (e.g. diabetes, high blood pressure, or heart and lung diseases) may be more susceptible to the impact of the coronavirus infection and at higher risk of mortality from COVID-19 (Wang et al. 2020; Yang et al. 2020); there is also evidence that racial and socioeconomic disparities may play a role (Brandt et al. 2020).

Because exposure to air pollution is also known to contribute to the development of such underlying diseases (Cohen et al. 2017; State of Global Air 2019), air pollution may increase susceptibility to morbidity and mortality from COVID-19, possibly in ways that we do not fully understand (Conticini et al. 2020). Early evidence from China reports an association between short-term exposure to air pollution and COVID-19 (Zhu et al. 2020), and preliminary, as yet unpublished, analyses in Italy and the United States report associations with longer-term exposure. HEI welcomes innovative proposals to study the differential effects of both short- and long-term exposure to air pollution on mortality and morbidity from COVID-19 in various population subgroups to better understand which subgroups are most vulnerable. Insights about these issues may inform public health responses to current and future outbreaks of COVID-19 or other diseases.

For both types of studies, it should be noted that there are challenges regarding quality of mortality and morbidity data. New ICD codes for COVID-19 were introduced in March, and it is not clear how consistently these have been implemented and how this has affected coding of other respiratory illnesses. Diagnostic testing has been applied at varying rates across and within countries. Undercounting of morbidity and mortality outside of hospitals continues to be a problem. In addition, researchers need to be aware that there may be novel confounders that need to be accounted for, and that may be transient in nature.

Additional research topics, such as the role of ambient particles in coronavirus transmission and mechanisms underlying SARS-CoV-2 health effects, will not be considered responsive to the RFA.

### **Budget and scope**

HEI is making \$2 million available for RFA 20-1B for one- or two-year studies with budget levels as outlined above.

Proposals must include a well-designed analytic plan, and documentation of access to suitable human health and air quality data that is sufficient to address the research questions and also confounding and effect modification due to age, socioeconomic status, occupational exposures, employment status, housing conditions (crowdedness, indoor air quality), noise levels, access to and usage of health care, among others. HEI is especially interested in proposals from investigators who have ready access to and experience working with existing population and exposure data that may facilitate timely and efficient conduct of the research. On the other hand, some studies may need to collect new data and develop new approaches and statistical methods to answer these complicated

questions; HEI will also consider proposals for such studies, within the budgetary and time limits stipulated above.

Studies that enable structured comparisons within and between countries with available high-quality air pollution and human health data, and which represent settings and conditions most often found in North America, Europe, and other developed countries, will be considered responsive.

## References

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

HEI will process applications with an expedited review schedule as detailed below.

The application process consists of two stages. The first stage involves the submission of a letter of intent, which is reviewed by the [HEI Research Committee](#) at its June meeting to ensure the application is responsive to the RFA. If the Research Committee determines the letter of intent to be responsive, then the investigator will be invited to prepare a full application. Full applications will be sent out for external peer review and discussed by the Research Committee at its October 2020 meeting. For particularly promising and timely proposals, the Committee may consider a fast-track review of full applications. Those researchers (if any) will be contacted in early July.

### LETTER OF INTENT

HEI requires applicants to send a two- or three-page Letters of Intent to provide information on the likely response to the RFA and to organize the application review process. It should include a synopsis of the project and study objectives, indicating the hypotheses to be addressed, qualifications of the team listing key members of the research team and their roles in the project, a list of all participating institutions, and access to relevant data (if applicable). An estimated total budget and study duration should be provided, choosing from the 2 options provided (i.e., a one-year or two-year study). In addition, brief biosketches (maximum 2 pages per person) of the principal investigator and key co-investigator(s) should be provided. Applicants can use HEI form F-8 or another format, as long as each biosketch is no longer than 2 pages. The letter and biosketches should be turned into a combined PDF before submitting. Confidential or proprietary information on methodologic details should not be included in the Letter of Intent.

### Deadline for Letters of Intent and Evaluation Process

Letters of intent should be submitted by e-mail in PDF format to [funding@healtheffects.org](mailto:funding@healtheffects.org) (subject line: *PI last name RFA 20-1B Letter of Intent*) no later than **JUNE 8, 2020**, with a copy to Ms. Lissa McBurney ([science-admin@healtheffects.org](mailto:science-admin@healtheffects.org)). HEI will acknowledge receipt of the application.

All letters of intent received by June 8 will be considered. Researchers who miss the deadline for submitting a letter of intent should contact HEI as soon as possible to determine whether their application can still be considered.

Letters of intent will be reviewed by the Research Committee at the end of June to determine relevance of the proposed research to the objectives of the RFA. If a large number of letters is received, it is at the discretion of the Committee to rank applications based on scientific merit and responsiveness to the RFA and invite a limited number of full applications. Applicants will be informed whether or not to submit a full application by early July. HEI may contact the applicant to advise him or her about how to make the application more responsive to the specific objectives of the RFA. For questions contact HEI at [funding@healtheffects.org](mailto:funding@healtheffects.org).

### FULL APPLICATION

HEI will invite selected applicants to submit a full application. The full application should describe, 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 turned into a combined 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 proposal, see [www.healtheffects.org/research/investigators/commitments](http://www.healtheffects.org/research/investigators/commitments).

The full application should be prepared based on a tentative start date of February 2021, pending contract negotiation (see [www.healtheffects.org/research/investigators/commitments](http://www.healtheffects.org/research/investigators/commitments)) and approval by the applicant's Institutional Review Board.

### **Deadline for Full Applications**

Invited Full Applications for RFA 20-1B should be submitted to [funding@healtheffects.org](mailto:funding@healtheffects.org) (subject line: *PI last name RFA 20-1B Full application*) no later than **SEPTEMBER 9, 2020**. 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 the end of October, 2020.

### **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.

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