RFA 23-1: ASSESSING HEALTH EFFECTS OF TRAFFIC-RELATED AIR POLLUTION IN A CHANGING URBAN TRANSPORTATION LANDSCAPE

INTRODUCTION

The Health Effects Institute (HEI) is seeking to fund studies to assess health effects of long-term exposure to traffic-related air pollution (TRAP). Studies should propose novel or improved methods and approaches to evaluate exposure to traffic-related air pollutants as technologies and fuels change, the fleet turns over, mobility transforms, and electrification makes greater inroads. New research in this area was identified as one of the priority areas in HEI's Strategic Plan 2020-2025. The development of this RFA was informed by HEI's Special Report 23, *Systematic Review and Meta-analysis of Selected Health Effects of Long-Term Exposure to Traffic-Related Air Pollution*.

STUDY DURATION AND BUDGET GUIDELINES

Overall, a total of $5 million will be available for this RFA. HEI expects to fund a small number of studies (2 to 3 years in duration). Preparation of the final report should be included in the budget and timeline of the final year of the study.

BACKGROUND AND RATIONALE

The health effects of TRAP continue to be an important public health interest across the globe, with highest exposures in urban settings and residences in proximity to busy roadways. In conservative global estimates, vehicle tailpipe emissions were associated with an estimated 361,000 deaths in 2010 and 385,000 in 2015 (Anenberg et al. 2019). The World Bank Group estimated 184,000 deaths worldwide in 2010 attributable to TRAP as indicated by $PM_{2.5}$ derived from vehicular emissions (Bhalla et al. 2014). Similarly, Lelieveld and colleagues (2015) estimated that TRAP is responsible for one-fifth of deaths from air pollution in the United States, the United Kingdom, and Germany.

TRAP is a complex mixture of gases and particles resulting from the use of motor vehicles. Motor vehicles emit a variety of pollutants, including nitrogen dioxide (NO_2), elemental carbon (EC), ultrafine particles (UFP), and other components of particulate matter ≤2.5 μm in aerodynamic diameter ($PM_{2.5}$). When emitted through vehicle exhaust, these pollutants are called tailpipe emissions. When emitted by other means, such as evaporative emissions of fuel, the resuspension of dust, the wear of brakes and tires, and the abrasion of road surfaces, they are called non-tailpipe emissions (Frey 2018; Harrison et al. 2021; HEI 2010a).

In 2010, HEI published a comprehensive review that drew conclusions about whether the associations between exposure to TRAP and health outcomes were causal, evaluating both toxicological and epidemiological evidence. At that time, it was concluded that the evidence was sufficient to support a causal relationship between short- and long-term exposure to TRAP and exacerbation of asthma in children. Furthermore, the 2010 review documented evidence deemed "suggestive" of a causal relationship between exposure to TRAP and other outcomes, including all-cause and cardiovascular mortality (HEI 2010a).

Since the 2010 HEI review, many additional studies investigating the health effects of exposure to TRAP have been published, exposure assessment has been enhanced, and regulations and vehicular technology have advanced significantly. Therefore, HEI formed a new Panel, consisting of 13 experts in epidemiology, exposure assessment, and statistics to conduct a new review. The objective of the review was to evaluate systematically the epidemiological evidence regarding the associations between long-term exposure to ambient TRAP and selected health outcomes. The resulting HEI Special Report 23 was recently published (HEI 2022), along with a short communication paper of the main findings (Boogaard et al. 2022). The new Panel found a high level of confidence that strong connections exist between TRAP and early death due to cardiovascular diseases. A strong link was also found between TRAP and lung cancer mortality, asthma onset in children and adults, and acute lower respiratory infections in children. The Panel's confidence in the evidence was considered moderate, low, or very low for the other selected outcomes, such as coronary events, diabetes, and adverse birth outcomes. Several challenges and future research opportunities emerged from the findings of the review; some of them are discussed below.

Traffic-Related Air Pollution

Exposure assessment of TRAP is challenging; TRAP is a complex mixture of many particulate and gaseous pollutants and is characterized by high spatial and temporal variability. There is still no pollutant fully traffic-specific, as the pollutants emitted by motorized traffic are also emitted by other (combustion) sources. Many pollutants are considered to be related to traffic based on previous emissions, monitoring, and modeling studies, such as NO_2, EC, $PM_{2.5}$, UFP, heavy metals, polycyclic aromatic hydrocarbons, and volatile organic compounds.

Emissions from motorized traffic can affect air quality at the local (< 1 km), neighborhood (1-5 km), urban (5-50 km), and regional (>50 km) scale. The highest direct exposure to TRAP occurs at the local scale, that is, when a person is in transit (walking, cycling, or travelling in a vehicle) or living or working close to major roads. The rate at which vehicle emissions disperse into ambient air depends on multiple factors that are highly variable, including wind speed, wind direction, temperature, atmospheric stability, terrain, land use, and buildings and other structures. In addition, air pollution from other sources—such as from industry, coal combustion, biomass burning, and agricultural sources, as well as from atmospheric transport of pollutants from distant sources—contributes to the overall air quality. The results of these emissions are elevated concentrations of air pollutants through primary emissions and through the formation of secondary pollutants, such as secondary PM and ozone. People are exposed to these air pollutants when outdoors or indoors through the infiltration of outdoor air pollutants. Human exposures are also determined by various dynamic factors, such as mobility patterns and distance from the source (HEI 2022).

A range of models, such as dispersion, land use regression, and hybrid models, have been developed to estimate exposure to TRAP. Moreover, novel measurement technologies—such as air pollution sensors, mobile monitoring, location tracking, and other technologies—are increasingly used to measure TRAP and time activity. Each of these exposure estimation approaches has limitations discussed in HEI's Special Report 23. There remains a clear need to improve methods to assess exposure contrast from TRAP and other sources for key traffic-related pollutants for health studies. HEI issued RFA 19-1, *Applying Novel Approaches to Improve Long-Term Exposure Assessment of Outdoor Air Pollution for Health Studies*, to harness novel measurement technologies—such as air pollution sensors, mobile monitoring, and location tracking—and modeling approaches, such as hybrid models and machine learning approaches.

Because TRAP is a complex mixture, a key question that remains largely unresolved so far is whether one or more of the TRAP indicators can be shown to have health effects independent of the other traffic pollutants. In HEI's Special Report 23, the individual pollutants—including NO_2—were considered as indicators of the TRAP mixture and hence does not answer this question. The Committee on the Medical Effects of Air Pollutants in the United Kingdom (COMEAP 2018) attempted to address this question for NO_2 and mortality. Perhaps not surprisingly given the often-high correlation in space and time between NO_2 and other traffic-related air pollutants, as well as other challenges, COMEAP members were unable to reach a consensus view regarding the causality assessment for NO_2.

NO_2 was the TRAP exposure indicator most widely used in the health studies identified in HEI's Special Report 23, followed by EC and $PM_{2.5}$. Few long-term health studies were identified for some pollutants, particularly UFPs and non-tailpipe PM indicators, and such studies were identified as a future research need. The lack of studies investigating long-term exposure of UFP—partly due to the lack of comprehensive monitoring—was also flagged in HEI's Perspectives 3, *Understanding the Health Effects of Ambient Ultrafine Particles*, and multiple HEI studies are currently underway addressing this research gap. Furthermore, HEI issued RFA 21-1, *Quantifying Real-World Impacts of Non-Tailpipe Particulate Matter Emissions,* to evaluate real-world exposure indicators of non-tailpipe PM emissions from motor vehicles and to assess the effects of such emissions on air quality, exposure, and health. Interest in the contribution of non-tailpipe emissions to air quality and health is increasing across the globe given the push towards electrification of the fleet and that regulations continue to be targeted almost exclusively on tailpipe emissions (Piscitello et al. 2021). Non-tailpipe emissions comprise particles in a broad range of sizes—including the coarse, fine, and ultrafine ranges—but compared with tailpipe PM emissions, they are generally in the larger size range and have less carbonaceous material and a higher metallic content (Liati et al. 2019; Nosko et al. 2017). Hybrid and electric cars might produce greater amounts of tire wear because they are heavier and have higher torque than internal combustion engine cars, although the use of regenerative braking would likely reduce both brake and tire wear because it would reduce slippage between surfaces (e.g., at the tire-road interface). However, the estimates of such emissions and experimental data vary widely (Beddows and Harrison 2021; Liu Y et al. 2021; Timmers and Achten 2018).

A Changing Transportation Landscape

Tailpipe emissions from motor vehicles and ambient concentrations of most monitored traffic-related pollutants have decreased steadily over the last several decades in most high-income countries. This trend is a result of air quality regulations and improvements in fuel and vehicular emission-control technologies and is likely to continue (HEI 2022). At the same time, however, air pollution levels have not decreased equitably over time for all population groups in high-income countries (Clark et al. 2014; Clark et al. 2017; Liu J et al. 2021; Rosofsky et al. 2018). It has long been known that in many settings, marginalized communities are disproportionately exposed to air pollution, resulting in health disparities (Hajat et al. 2015; O'Neill et al. 2003). Furthermore, in most middle- and low-income countries, TRAP emissions trends have shown increases during the past decade and deserve more attention (Frey 2018; ICCT 2019).

A combination of new and emerging technologies, such as electric and autonomous vehicles, digital connectivity, and artificial intelligence, are laying the foundation for changes in the movement of people and goods (HEI 2022). Furthermore, a variety of new transportation and mobility trends is emerging particularly in high-income countries, mainly in response to the urgency of curbing greenhouse gas emissions from the transportation sector. For movement of individuals, mobility options are expanding from a traditional focus on private vehicle ownership and mass transit systems to include ride-hailing and car-sharing services, personal and shared scooters and bikes, and infrastructure to support walking and biking. At the same time, the adoption of virtual meeting technologies during the COVID-19 pandemic has substantially reduced commuting and business travel, possibly permanently. For movement of goods, an emphasis on rapid home delivery has driven major shifts in warehousing and logistics while bringing more delivery trucks and vans into urban areas (NASEM 2021).

Trends toward electrification, self-driving vehicles, and other automated technologies are opening new opportunities and tradeoffs. They offer alleviation of some components of TRAP because of the high efficiency of such powertrains and the absence of combustion emissions at the site of use. Electric vehicle sale is growing rapidly as technical and infrastructural barriers are overcome, and government policies and manufacturers' pledge to boost their adoption come to fruition, though adoption differs widely within and across countries across the globe (HEI 2022).

Despite this momentum, it is important to note that there are still several barriers to overcome, such as the slow development and cost of battery technology and building a dense charging infrastructure. Moreover, the full benefits of electrification will be realized only by concomitant decarbonization of the electric grid (Requia et al. 2018). There are also environmental and health concerns regarding the use and disposal of batteries, which use such metals as nickel, lithium, manganese, and cobalt, and current battery design does not allow for ready recycling (Morse 2021). Additionally, it is important to note that vehicle fleets turn over at a slow rate, and there are numerous other forces at play that would influence such a transition, including fuel prices and incentive policies. A recent analysis highlighted the role of existing and emerging fuels and technologies in commercial trucks, transit, and school bus fleets (Diesel Technology Forum 2022). Another study evaluated several approaches to reducing greenhouse gases and other emissions from medium and heavy-duty vehicles from 2022-2032 and finds advantages with advanced diesel technology, particularly when using renewable biofuels as compared to an electrification strategy during the same time period (Stillwater Associates 2022).

In light of such uncertainties, some organizations are circumspect in their projections. For example, the U.S. Energy Information Administration in its most recent Energy Outlook (U.S. EIA 2022) estimates that electric and hybrid vehicles will make up only about 21% of light-duty sales in the United States by 2050; 9% of the total light-duty vehicle fleet would be electric and hybrid by 2050. Other forecasts are much more favorable: electric vehicles would account for 20% of global light-duty vehicle sales in 2025, and up to more than half of the global light vehicle sales by 2035 (BCG 2022). Unsurprisingly, internal combustion engine vehicles will continue to be a part of the fleet for some decades to come. Even more so in low- and middle-income countries, partly due to current—largely unregulated—practice where millions of used (older, more polluting) vehicles are exported every year from the United States and Western Europe (UNEP 2021).

Given all the uncertainties, any predictions about the future of new transportation and mobility scenarios on TRAP and health impacts are at best speculative. If the promises of new transportation and mobility scenarios are realized, they might deliver many benefits, including more efficient driving and fuel savings, increased speed, congestion mitigation, reduced vehicle ownership, and higher occupancy, along with the accompanying improvements in efficiencies for individual drivers and the transportation sector as a whole. These developments will result in reductions in TRAP and greenhouse gas emissions and exposures, particularly as vehicle electrification spreads. On the other hand, technology penetration is never straightforward and is impossible to predict. There is the potential danger that these developments might be accompanied by increased travel demand and delivery services, with a reduction in active transport and the use of public transport. Moreover, the benefits of new transportation and mobility might not accrue to everyone. Marginalized communities might even experience additional air pollution-health inequalities, due to residential displacement of these communities or inequitable placement of facilities and services in them (NASEM 2021). Such changes might even lead to more vehicles and traffic congestion, reductions in physical activity, and increased emissions, exposures, and associated adverse health effects in some settings (HEI 2022).

The air pollution epidemiology studies—the basis for the review of selected health effects of long-term exposure to TRAP in HEI's Special Report 23—are by design retrospective. They provided valuable information about the (recent) past but might not represent the impacts of lowered exposures from today's vehicles nor predict the health effects of future reductions in TRAP due to the adoption of new transportation and mobility options. Burden of disease and health impact assessment approaches have emerged to fulfill that role. For example, burden of disease estimates seek to quantify the mortality or morbidity attributable to long-term exposure to "current" levels of TRAP (e.g., Annenberg et al. 2019; Bhalla et al. 2014; Lelieveld et al. 2015). In contrast, health impact assessments seek to estimate the health benefits likely to arise under plausible alternative scenarios, such as from the future implementation of new technologies and policies (e.g., Malmvist et al. 2018; Minet et al. 2021; Smargiassi et al. 2020). Policy scenarios of interest could include analysis of impact on health from various fleet compositions, the rate of fleet turnover for newer technologies, and level of compliance with current regulations.

A Role for Accountability Research

Assessing health effects of air quality interventions is of ever-increasing interest, and HEI has a longstanding commitment to accountability research. Accountability research refers to empirical studies assessing the effects of regulatory actions, other interventions, or "natural" experiments on air pollution and health (sometimes also referred to as intervention studies). In 2003, HEI defined a conceptual framework (also referred to as the full-chain approach) for accountability research, where interventions are assessed at different stages, including emissions, concentrations, exposures, and health effects (HEI Accountability Working Group 2003). Based on that framework, HEI has funded an extensive program of about 20 studies to date, with varying scopes and methods. HEI developed other publications that summarized the results, challenges encountered, and lessons learned and have provided possible directions for future research (e.g., Boogaard et al. 2017; Burns et al. 2020; HEI 2010b; van Erp and Cohen 2009). HEI issued RFA 18-1, *Assessing Improved Air Quality and Health From National, Regional, and Local Air Quality Actions*, to fund studies to assess the health effects of air quality actions, with a particular focus on long-term complex regulatory programs, interventions at the local level and around ports and major transportation hubs and corridors.

A recent paper summarized the body of evidence that investigated the effectiveness of past, current, or future urban policy interventions to mitigate traffic to reduce TRAP and improve public health (Khreis et al. 2022). They captured a broad suite of interventions related to pricing, land use, infrastructure, behavioral, technology, fleet management, and fuel and emission regulations or restriction of vehicles. They identified 58 unique urban policies and a total of 1,092 unique policy scenarios. Most of the studies evaluated the effect of the intervention on traffic emissions, only about 10% documented the effect on TRAP exposure, and even fewer (about 3%) adopted a full-chain approach, which included a health component. As also identified in HEI's Special Report 23, there is a clear need for additional studies to evaluate the effectiveness of key measures to reduce TRAP and improve public health, as well as to assess the health benefits of measures designed to mitigate traffic or achieve other policy objectives. The measures might include a broad suite of urban policy interventions to improve air quality and climate, including opportunities for physical activity and active transport to mitigate the adverse health effects of TRAP, as well as electrification of the vehicle fleet. These measures might also include an array of measures designed to decrease air pollution-health inequalities in marginalized communities.

Complex Interplay Among Factors That Influence TRAP And Health

With the changing transportation and mobility landscape, there is a better appreciation that transportation affects health in numerous ways. Emerging knowledge suggests that transportation can affect health through many intertwined pathways, such as traffic accidents, noise, climate change, temperature, stress, and the lack of physical activity and green space (Glazener et al. 2021, and Figure 1). These environmental, social, and behavioral factors might either confound or modify the health effects of TRAP in populations. Further, some communities might be disproportionately exposed to multiple, overlapping factors due to the placement of or proximity and access to transportation facilities, services, infrastructure, and activities.

HEI's Special Report 23 focused on the health effects of TRAP, although consideration was given to other related factors, most notably traffic noise. However, only a few TRAP and health studies adjusted for traffic noise (about 7% of total studies included in the systematic review). Studies on the interactions of TRAP effects through other exposures such as noise, green space, temperature, and physical activity are relatively scarce but are needed as they reflect real-world conditions and could further advance our understanding of the implications of transportation activities on TRAP and health, and associated inequalities.

HEI issued RFA 17-1, *Assessing Adverse Health Effects of Exposure to Traffic-Related Air Pollution, Noise, and Their Interactions With Socio-Economic Status*, to fund TRAP and health studies that would evaluate interactions with spatially correlated factors, specifically traffic noise, socio-economic status, and green space. As the HEI studies near completion, valuable lessons learned might be integrated in new research.

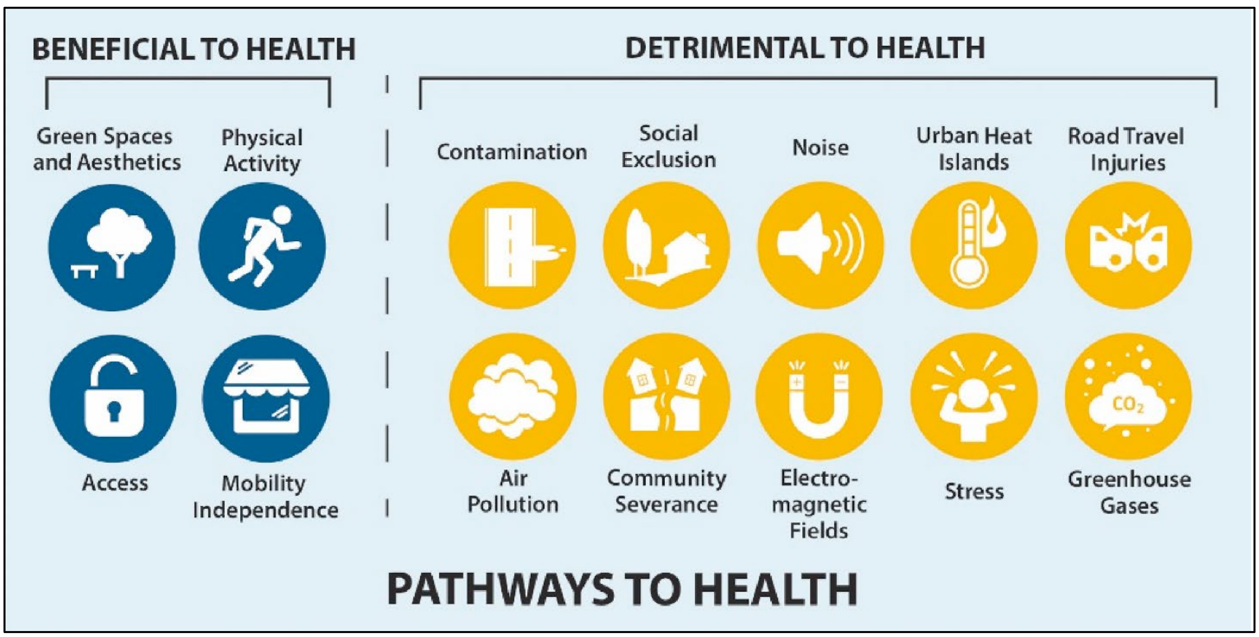

Figure 1. Pathways through which transportation influences health (source: Glazener et al. 2021).

A Need for TRAP and Health Studies in Low- and Middle-Income Countries

The majority of studies in HEI's Special Report 23 were conducted in Western Europe and North America. Studies in Asia (predominantly China) emerged more recently. The Panel identified a particular need for studies in low- and middle-income countries, where TRAP levels are typically higher, TRAP emissions trends have shown increases during the past decade, and adoption of new transportation and mobility trends are particularly slow or absent. Hence, a specific objective is dedicated to those understudied countries.

Many low- and middle-income regions are undergoing rapid urbanization and industrialization. In the last decade, motor vehicle ownership has increased across urban centers, and recent emissions inventories indicate increases in transportation-related emissions for both NO_x and $PM_{2.5}$, especially in Asian and African countries (McDuffie et al. 2020). Of note, in these regions, more people live closer to traffic sources, thus exposing them to higher levels of TRAP. Although cross-sectional or short-term studies are increasingly available, studies focused on long-term exposures to pollutants, including TRAP, remain limited (Baumgartner et al. 2020; Heydari et al. 2022).

Conducting high-quality research in those understudied regions could be particularly difficult due to various reasons, including lack of data, resources, and the necessary infrastructure. Hence, HEI expects that a capacity strengthening component will be built into studies in those regions, with close collaboration between researchers from low- and middle-income studies and colleagues from high-income countries.

OVERALL OBJECTIVES

HEI is seeking to fund studies to assess health effects of long-term exposure to TRAP. Studies should propose novel or improved methods and approaches to evaluate exposure to and health effects of traffic-related air pollutants as technologies and fuels change, the fleet turns over, mobility transforms, and electrification makes greater inroads.

SPECIFIC OBJECTIVES

HEI seeks to fund studies that can accomplish at least one of the objectives listed below. Note that in meeting the first three objectives, investigators should consider whether their work can effectively include effects in marginalized communities in high-income countries.

- In the proposed health studies, develop, validate, and apply novel or improved exposure assessment methods suitable for estimating exposures to traffic-related air pollutants that (1) account for other air pollution sources in urban areas (such as airports, (sea)ports, industries, and other local point sources), (2) could distinguish between tailpipe and non-tailpipe traffic emissions, to the maximum extent possible, and (3) take into consideration the overall impact of (new) transportation and mobility trends on air quality and exposure.
- Evaluate the effectiveness of key measures to reduce TRAP and improve public health, as well as to assess the health benefits of measures designed to mitigate traffic or achieve other policy objectives.
- Estimate the impacts on urban air quality and health of various new transportation and mobility scenarios, including a baseline (status quo or "business as usual") scenario.
- Investigate health effects of long-term exposure to TRAP in understudied low- and middle-income countries.

CRITICAL STUDY DESIGN CONSIDERATIONS

HEI considers the following features of the study design important to meet the overall objectives:

<u>Study populations</u>

The RFA targets urban populations because traffic emissions are an important source of urban air pollution, and these areas are rapidly growing. About two-thirds of the global population is estimated to reside in urban areas by 2050, with much of the growth in urban populations concentrated in Asia and Africa (United Nations 2018). Moreover, cities are at the forefront of innovation and major transportation and mobility changes.

Study designs

Various study designs, including cohort studies, case–cohort, case–control, accountability (intervention), and cross-sectional studies can be considered for these investigations. Studies without individual-level data (i.e., fully ecological outcome, exposure, and covariates data) are not considered responsive.

In case accountability studies are proposed, the applicant should ensure that substantial exposure reductions are expected, and—where appropriate—should include proper control groups. Please refer to a discussion of critical design considerations for accountability studies in HEI Communication 14 (van Erp and Cohen 2009) and Communication 15 (HEI 2010b).

HEI also welcomes burden and health impact assessments that investigate the "current" situation and alternative plausible alternative scenarios, such as from the future implementation of new technologies and policies. Life-cycle analyses are outside the scope of the RFA.

Geographic location

Studies in all urban regions of the world would be considered responsive.

Exposure assessment

Long–term exposure is defined as a duration of months to years, similar to the definition in HEI's Special Report 23 and the World Health Organization (WHO) Air Quality Guidelines update (WHO 2021). Studies should include current or more recent exposures (e.g., the past 5 years) to reflect the changes in concentrations and composition of TRAP associated with the rapidly changing transportation landscape.

Studies should include multiple pollutants as indicators of TRAP. Air pollutants to consider include NO_2, EC (which includes such related metrics as black carbon, black smoke, and PM absorbance), UFP, and markers of non-tailpipe emissions (e.g., specific metal [Fe, Zn] or organic components). Studies should also include $PM_{2.5}$ because it is regulated, although it is known to be a suboptimal surrogate. Inclusion of novel indicators and biomarkers of TRAP and mechanistic processes is encouraged (e.g., using omics approaches). Single-pollutant studies and studies assessing indirect traffic measures only (e.g., metrics based on distance and traffic density) will not be considered responsive.

Studies should develop and evaluate improved exposure assessment methods suitable to estimate long-term exposure to TRAP at relevant spatial and temporal scales for use in health studies.

Applicants should take into account other air pollution sources in urban areas, such as airports and (sea)ports in the exposure assessment methods. Local emissions, for example from restaurants and other point sources, are important when using fine-grid or receptor exposure models. In addition, in many urban areas, transported pollution from industrial and electric power sources can be important contributors and should be considered. The methods used to account for urban background concentrations will be carefully evaluated.

If measurement campaigns are proposed, studies should preferably use standardized and routine sampling methods. However, some studies might offer the opportunity to include novel measurement technologies, such as air pollution sensors, mobile monitoring or wearable devices. If such approaches are proposed, applicants should provide a rationale for their inclusion and demonstrated performance to measure the anticipated concentration ranges in the geographic or climatic area of application.

Health outcomes

Applicants should give a clear rationale regarding the choice of health outcomes in relation to earlier research, the research questions being addressed, and the relevance of such questions for policy.

Health effects or impacts of interest are all-cause and cause-specific mortality and morbidity endpoints, such as cardiovascular and respiratory outcomes, cardiometabolic outcomes, birth outcomes, neurodevelopmental outcomes, and neurodegenerative outcomes. Also, studies assessing life expectancy, years of life lost, and disability-adjusted life years will be considered responsive.

Inclusion of clinical and subclinical markers of disease to study the mechanistic pathways by which TRAP elicit adverse health outcomes will be considered responsive, such as pregnancy outcomes, lung function, blood pressure, and atherosclerosis.

Explore the role of other factors

Studies need to adjust TRAP health estimates for major potential confounders (e.g., age, smoking, socio-economic status) either by restriction or by direct or indirect adjustment approaches.

Studies should explore the role of other environmental, social, and behavioral factors that might either confound or modify the health effects of TRAP in populations, where possible. Such factors can include socio-economic status, traffic noise, green space, physical activity and diet, and high and low temperatures and other climatic conditions, including allergen exposure.

In particular, studies should examine how exposures and health effects are distributed by socio-economic and socio-demographic factors.

Precision and statistical power

Applicants should assess and discuss the expected precision and statistical power of their estimates, particularly because tailpipe emissions from motor vehicles and ambient concentrations of most monitored traffic-related pollutants have decreased steadily in most high-income countries. Assumptions needed for such calculations should be guided by relevant published literature.

Statistical methods

Applicants should propose appropriate statistical and analytical methods. Because model selection can affect the outcome, sensitivity analyses of the key modeling choices should be included.

To address the objectives of the RFA improved statistical approaches can be developed. Examples of areas where new and improved methods might be needed include

- Multipollutant or multi-exposure modeling approaches for estimating effects of TRAP (which is already a complex mixture) and other exposures (e.g., traffic noise, green space) and factors (e.g., socio-economic status) that might be highly correlated.
- Methods for indirect approaches to correct health effect estimates for important potential confounding variables, such as smoking.
- Statistical approaches that use alternative methods for confounder control (i.e., studies often referred to as causal modeling or causal inference studies).
- Use of new sensors and omics approaches that often have "big data" challenges to overcome.

RESEARCH TEAM

The research team should possess the full range of expertise to conduct the proposed research. The Principal Investigator (PI) must demonstrate a record of producing high-quality and objective research in areas relevant to the proposed work and be affiliated with an established research organization. The full team can include the PI, their immediate team (other faculty, research scientists, post docs, students, and technicians), co-investigators or collaborator(s) at the same or other institutions, and consultants. Researchers are encouraged to consult with government, policy experts, and urban planners to learn more about past, current, or future urban policy interventions to obtain a good understanding of the scope.

HEI strongly encourages applicants to diversify their research teams by including individuals from groups that are underrepresented in environmental assessment and health research and, to the extent appropriate for the study location(s), attuned to and knowledgeable about the communities in which the studies will take place. For this purpose, HEI has adopted the National Institutes of Health definition of underrepresented populations in the U.S. Biomedical, Clinical, Behavioral and Social Sciences Research Enterprise.[1] The team's technical proposal ideally will be informed by engagement with experts who represent multiple sectors (e.g., academia, communities, regulatory and public health agencies, industry, and non-governmental organizations) and will include them in research, as appropriate. Additionally, the team should include as key members researchers from countries where the analysis is proposed, especially if the work is in understudied low- and middle-income countries.

The proposal must clearly identify each team member, their affiliation, and role in the research. The team should have access to study sites (as evidenced by letters of support in the proposal, if applicable) and have or obtain access to facilities, equipment, and instrumentation needed to support the proposed research. If investigators plan to use data or materials (e.g., filter samples) from previous research, 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. The application should include a letter from the investigator who owns the data or the materials that states willingness to share the data with the applicant and with HEI, if requested.

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 a long-standing 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. Please refer to here for the HEI Policy on the Provision of Access to Data Underlying HEI-Funded Studies.

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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[1] The National Institutes of Health definition of underrepresented populations includes individuals from racial and ethnic groups underrepresented in health-related sciences on a national basis, individuals with disabilities who are defined as those with a physical or mental impairment that substantially limits one or more major life activities, and individuals from disadvantaged backgrounds, recognizing that women from these three backgrounds face particular challenges at the graduate level and beyond in scientific fields (Source: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-20-031.html).

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The submission and review of applications for RFA 23-1 will entail a two-stage process.

- Investigators should submit **a Preliminary Application by March 15, 2023**. The HEI Research Committee will discuss the preliminary applications and invite a limited number of investigators to submit a full application. Feedback will be provided late April.
- Invited investigators should submit **a Full Application by July 7, 2023**. Full applications will be reviewed by a Special Review Panel before consideration by the Research Committee. Applicants will be notified about the funding decision by October 31, 2023.

PRELIMINARY APPLICATION

Applicants should submit a brief Preliminary Application that provides the following information: title, abstract, scientific rationale, a brief description of the study aims, design and methods, and anticipated results. The Preliminary Application should also briefly discuss the applicant's qualifications and include a biographical sketch for each co-investigator (maximum two pages per person). An estimated total budget and study duration should be provided. No detailed budget forms are needed at this stage.

The preliminary application should not exceed **4 pages** (excluding references and biosketches) using the form provided on the HEI website. Please note that the required font size is 11 point with 1-inch margins.

Submission and Deadline

Preliminary applications should be submitted electronically to funding@healtheffects.org no later than **March 15, 2023**. HEI will acknowledge receipt of the application. Questions regarding the applications should be directed to Dr. Hanna Boogaard (jboogaard@healtheffects.org).

FULL APPLICATION

Invited full application should 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. Where applicable, a letter from the investigator who owns the data should be submitted and state their 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). 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 and consult the Instructions for Completing the Application. Application forms can be downloaded from https://www.healtheffects.org/research/funding. Please note that the required font size is 11 point with 1-inch margins. Form F-12 is separated from the rest of the application upon receipt. The data are kept confidential and not considered for funding decisions; HEI strongly appreciates completion of this form to track diversity of applications and funded investigators in an effort to continue to invest in, and expand HEI's investment into diversity, equity, and inclusion (DEI) efforts as part of its 2020 commitment. The application forms should be turned into a PDF with appropriate bookmarks before submitting.

Deadline for Full Applications

Invited Full Applications should be submitted to funding@healtheffects.org no later than **JULY 7, 2023**. The application should be in PDF format with a maximum file size of 20 MB. HEI will acknowledge receipt of the application.

Full applications without pre-submission of a preliminary application and invitation from the Research Committee will not be considered.

RFA 23-1: EVALUATION PROCESS FOR FULL APPLICATIONS

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 might 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 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 PI, 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

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 and address 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.

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.

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.

For Review Panel members and Research Committee members, in some situations it might 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, they are expected to recuse themself from the review of the application(s) at issue.