

APPENDIX A: EXERPTS OF HEI STATEGIC PLAN 2020-2025 (Revised draft December 2019)

“Informing Air Quality and Health Decisions for 2020 – 2025...and Beyond”

Moving forward, HEI sees this theme to be integrated into four core program elements and one major cross-cutting theme:

- *Accountability: Testing the Links Between Air Quality Action and Health* – building on HEI’s accountability studies on key actions to improve air quality, exploring questions such as better methods for testing such links, whether such research help us test for causality and how they might help improve cost and benefit analyses for future actions. Studies soon to be initiated under a new Request for Applications (RFA) will address some of these questions but, given the complex nature of this issue, more research is clearly needed. In particular, we will examine how best to assess the effectiveness of further air quality improvements at low ambient concentrations.
- *Complex Questions for the Air Pollution Mixture* – The difficult issues surrounding the complex air pollution mixture continue to challenge scientists and decision makers alike. HEI’s Low Level Studies are testing concentration response relationships at the lowest levels and HEI’s new RFA on exposure will seek and launch studies using sensors and many other new techniques to measure exposure to hard to characterize pollutants (NO_x, UFP, etc.).

To shed better light on the many questions that such research is raising, HEI will – at the earliest stages of the new Strategic Plan - ask experts to answer the question *Where can science best contribute?* Are there mechanistic studies needed to better understand complex exposures, and/or should HEI re-visit PM component and source-specific exposures and their differential effects? Are there new more effective techniques to accomplish this?

- *Transport and Urban Health* – A host of new innovations and other changes are making inroads and changing the future of transportation, even as the internal combustion engine will be in use for many years, and issues of in-use, sea- and airport emissions, non-tail-pipe, and other emissions continue to arise. New questions are arising in this context, such as the health effects of ultrafine particles (UFP), as well as the role of factors such as noise, socioeconomic status, and access to green space. Anticipating the many diverse and potentially disruptive changes in transport, targeting the most significant continuing questions, and placing transport in the broader setting of urban health, will be key priorities for HEI going forward.
- *Global Health:* In the developing world, especially India and China, and elsewhere in Asia, rapid growth has raised levels of air pollution from all sources, and health science and policy decisions are just beginning to catch up to the challenge. With additional funding, HEI will continue and enhance its world-leading efforts to produce and communicate the results of Global Burden of Disease from outdoor air pollution, and produce improved science on the health effects of air pollution in developing countries, and a global analysis of the contributions to air pollution burdens from each source for every country in the world (GBD-MAPS Global).
- *A Key Cross-Cutting Issue:* Along with the opportunities mentioned above, we have identified a number of other issues that cut across our programs. Most prominent among such issues is *Transparency in Policy-Relevant Science* which has three major components:
 - *Data access and transparency* are essential to the scientific process, providing insight into analytical and methodological details. Making data and analytical methods available

allows others to replicate study results independently and, where necessary, perform alternative or additional analyses. As such, transparency provides equally valuable feedback to the decision-making process. HEI maintains a strong policy on facilitating access to underlying data and methods for the studies it funds; this will be a hallmark of the HEI Strategic Plan 2020–2025.

- *Systematic review* of the scientific literature. The process for performing and synthesizing reviews has been evolving and currently the use of *systematic* review protocols has been emphasized in the environmental health context. HEI is implementing these enhanced efforts in its reviews of the traffic literature and will target ways to further enhance these practices in 2020-2025.
- *Testing and Evaluating Statistical Methods* has been a hallmark of HEI's implementation of all of its research programs. This effort will continue in 2020-2025 with particular emphasis on new methods for causal inference and other enhanced statistical techniques

We also expect to pursue important cross-cutting issues in all of our efforts, including selected *at-risk populations* (e.g., the elderly, the young and those with pre-existing diseases; and those who may be more highly exposed and/or more vulnerable due their socioeconomic status) and *enhanced exposure assessment; new biologic techniques, and new health endpoints.*

While the HEI Strategic Plan is designed to be a clear path forward for HEI to follow in the coming years, we have found that, in order to be as responsive as possible to the emerging needs of our sponsors and others, we must as well build in the flexibility to *anticipate and act on the unanticipated*, and fully expect to continue to have that capacity in the coming years.

The next two sections describe in detail the rationale for selecting these four topics and the approaches that HEI will take in addressing them (*Priority Research Opportunities*), and the timetable for implementation (*Implementing the HEI Strategic Plan 2015-2020*).

What Will HEI's 2015-2020 Plan NOT Address?

As is inevitably the case when a science organization has to make choices about where to focus its resources, HEI would, in its new Strategic Plan, choose to *not* pursue certain issues that we have considered and /or that others have proposed:

- HEI will not, in the coming years, pursue major new programs of research on individual pollutants or categories of pollutants (e.g., individual criteria pollutants or individual air toxics), but focus instead on multipollutant studies of exposure and health, whether in toxicology or in epidemiology at the local, regional, and national scale.
- While HEI will include possible implications of climate change as a modifier of air pollution effects, we would not expect to engage in broader research on the direct health effects of climate change (e.g., concerning sea level rise or changes in the spread of vector-borne diseases).

THE MAJOR RESEARCH OPPORTUNITIES

HEI envisions working on the following four main areas of research:

- Accountability: Testing the Links Between Air Quality and Health (page 3)
- Complex Questions for the Complex Air Pollution Mixture (page 4)
- Transportation and Urban Health (page 7)
- Global Health (page 10)
- As well as Cross-Cutting Issues (page 12)

Accountability: Testing the Links Between Air Quality Actions and Health

HEI has a longstanding commitment to accountability research. Accountability studies evaluate the effectiveness of actions to improve air quality, providing a critical feedback loop to decision makers.

HEI's interest and commitment to accountability studies stems in large measure from the importance of assessing whether complex policies and actions, and other interventions, are actually yielding the improvements in air pollution and public health that were initially projected. Given that air quality has improved over the past decades, further improvements become more difficult to achieve and more costly. Early on, HEI defined initial concepts and methods with the publication of a major Monograph. Since then, HEI has funded two successful waves of studies that evaluated both local interventions occurring over relatively short periods of time as well as more complex, longer-term interventions at the regional or national level. Lessons learned about the effectiveness of various approaches from these studies can inform the design and implementation of future efforts to improve air quality.

Currently, HEI has embarked on a third wave of studies that are expected to start in early 2020. RFA 18-1 identified the following areas as of high priority for further research: studies that evaluate policies and actions at the national or regional level implemented over multiple years; interventions at the local (e.g., urban or regional) level; studies focused on schemes to improve air quality around major ports (marine and air) and transportation hubs and corridors; and statistical methods development.

Looking ahead to the 2020–2025 Strategic Plan, HEI plans to continue its leadership role:

New Accountability Research

*HEI will strengthen its leadership in conducting Accountability studies of the **air quality and health impacts of air quality interventions**.* After completing 13 seminal studies during the last decade and publishing reports and papers about accountability research, a new program of research — with up to six studies funded under RFA 18-1 (see above) to be launched in early 2020 — is setting the stage for the next generation of accountability research during the core years of HEI's new *Strategic Plan 2020–2025*. Such studies are a key underpinning of smart policy and regulation. They provide one of the few avenues for rigorously testing the links between emissions, exposure, and health. In addition to evaluating the air and health consequences of air quality regulatory actions,

this program also aims to develop more robust research designs and statistical methods for estimating the health effects of air quality interventions.

New Methods:

HEI continues to foster development of new statistical methods to enable direct evaluation of well-defined, long-term regulatory interventions. An important question that will be included in further thinking on accountability is how to assess the effectiveness of further air quality improvements at very low ambient pollutant levels. Because the effect on health of further reductions in air pollution are likely to be small, particularly in high income countries with low ambient levels, it is important to develop a sophisticated perspective on whether future studies will have the power to detect and quantify an effect — if there is one — and to describe a null effect with enough precision to be informative for policy purposes. It will be critical to pay serious attention to the sensitivity of statistical inference to model specification and time-varying confounding or implement quantitative bias analyses. Where possible, HEI is asking researchers to evaluate whether their study can add to the evidence base for a causal relationship between air pollution and health.

Specific Study Areas:

- National- or regional-scale air quality actions over the long term. In the US, the EPA and other agencies have promulgated on-road and off-road diesel rules, rules covering locomotives and marine vessels, standards for utilities and industrial boilers, and interstate rules. Similar efforts are taking place in Europe and Asia. HEI is considering funding a several new studies of major interventions at different geographic locales; proposals for such studies are currently being reviewed by HEI and new studies are expected to start early during this *Strategic Plan period*.
- Air quality actions at the local (urban) scale. Recently, many cities have started to implement actions to improve air quality, e.g. congestion charging and low emission zones, limiting driving days for cars with certain license plate numbers, implementing road closures or restricted access of certain streets (e.g. Oxford Street in London), or outright bans of certain vehicles, for example diesel vehicles, mainly in Europe. These actions go hand in hand with efforts to transform urban mobility. Those new developments lead to growing attention on the fuller range of potential effects of transportation and mobility decisions on public health, including the positive effects of an increase in physical activity. Among the studies under consideration for funding include studies of local and state traffic and other interventions and their implications for air quality and health.
- HEI also expects to seek out and support other relevant areas identified by investigators and stakeholders.

Complex Questions for the Air Pollution Mixture

A number of questions regarding the air pollution mix have long been a central theme of HEI's research and review activities and we plan to continue our focus on such issues. 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 technological improvements. The levels of many ambient pollutants today are 60 percent or more lower than the levels 25-30 years ago, and concentrations of hazardous air pollutants have seen even steeper declines, sometimes by as much as two orders of magnitude, over the decades. Yet, air pollution problems continue to be of public health significance and interest remains very high among the policy and research communities for a better understanding of exposures and health effects. In this context, the following factors are noteworthy:

- A relationship between exposures to low levels of air pollution – even below the current standards – and health effects is being reported in several new epidemiological studies, including early papers from two studies being funded by HEI. Using sophisticated new techniques for exposure assessment at very large geographical scales and health databases containing tens of millions of records, as well as developing new methods for meticulous statistical analyses, these findings raise questions about the level of protection offered by the current standards, at least for PM_{2.5}, and probably for ozone and NO₂ as well.
- HEI's NPACT studies were a systematic, multidisciplinary program which used coordinated toxicology, epidemiology and exposure assessment research to examine and compare the toxicity of PM components. The results of these studies suggested that none of the particle components could be definitely excluded as having no health effects, thus supporting the current regulatory approach of targeting the entire PM mix. Yet, given the varied approaches that can be, and are, used to control emissions from different sources, interest remains high in source and composition contributions to toxicity of PM. Interest also remains very high in other characteristics of PM, particularly size.

These and similar challenges point to the need for carefully crafted and well thought through research programs to address them, and present opportunities for HEI to design research and review activities to answer them.

Health Impact of Exposure to Low Levels of Air Pollutants:

HEI will complete, within the first years of the new *Strategic Plan*, its health effect studies of low-level exposure, applying innovative exposure and analysis techniques, examining PM, ozone, and NO₂ effects at low ambient levels, in the United States, Canada and Europe. HEI's pathbreaking program of these major studies in millions of participants will produce important new findings that will inform decisions by public health and environment agencies and by WHO on Global Air Quality Guidelines, as well as future estimates of benefits from air pollution reductions. These studies will also pave the way for novel methodologic advances in air pollution studies for years to come.

- **Testing the robustness of the findings:** As the first step after the initial completion and intensive HEI review of the low exposure studies, HEI will fund a modest effort to test whether their findings are reproducible using different statistical approaches. The three HEI funded studies have used somewhat different methods for their exposure assessment, health outcomes, and statistical analyses, raising the question of whether their results will be robust to analyses using alternative methods. HEI believes that the unprecedented efforts to gather comprehensive information on tens of millions of participants and their exposure will provide opportunities to apply the same or similar methods for exposure assessment for comparison among the different studies, best ways to address confounders and measurement error, and other analytical approaches, including methods for causal inference, and many additional questions.
- **Synthesis of Information on Health Effects at Low Exposures:** As with all HEI funded studies, the final reports from the low exposure studies will be subjected to stringent review; the review panel will prepare a commentary on each report. We also believe that the results of these studies – along with a few others, also examining effects at low levels – provide an excellent opportunity for a synthesis of all the information in this area. Working either with one of HEI's existing committees or a separate panel, HEI will prepare and publish such a synthesis during the far years of the grant.

Asking a Key Question: *Where can Science Best Contribute?*

In the past decades, the science on health effects of exposure to air pollution has made great strides. Scientific studies using epidemiologic, clinical, toxicologic, and mechanistic studies have provided valuable information which forms the basis for policy actions, leading to a reduction in ambient air pollution and improved human health. The observations of health effects at levels below the current NAAQS raise important new questions, which also present novel challenges for the currently available methods and approaches. To gain some insight on these issues and how research programs may be developed to answer them, HEI plans to form a special panel in the first year of the new Plan, composed of experts in toxicology, mechanisms, genetics, exposure generation, and other disciplines, and seek their guidance on how HEI might research the following kinds of questions:

- **Biological Plausibility of the Effects at Very Low Exposure Levels:** The observation of associated health effects in epidemiology analyses in low exposure studies raise questions of the biological/toxicological mechanisms that may operate under chronic, low exposure conditions. Though toxicological and mechanistic confirmation of effects is not essential for evaluating epidemiologic observations, such information can contribute to assessment of the broader weight of evidence for plausibility and causality, as has been the case documented in many EPA and WHO documents summarizing science in specific areas. How might these questions be addressed? Of necessity, traditional toxicology and mechanisms studies are performed at relatively high exposures. Are there new in vitro technologies that may be applied to capture changes at low levels of exposure? The answer to these questions is not straightforward and insights of the panel should provide valuable guidance to ensure that HEI makes the most effective research investments in this important area.
- **Characteristics and toxicity of PM:** Another very important issue where insights from the panel would be very useful is motivated from the intense interest, and potential policy decision value, regarding whether any specific characteristic of PM confer differential toxicity, which could lead to actionable control strategies. Embedded in this issue are questions regarding sources of PM (e.g., mobile vs stationary vs. biogenic, and chemical composition), size characteristics (e.g., ultrafine, fine and coarse particles), other properties (such as surface area, surface charge), nature of PM (e.g., freshly emitted PM, SOAs, aged PM), and many others, which might independently cause effects, or modify effects to different degrees. Given that epidemiological studies on such questions are very difficult and past studies have not provided clear cut answers, HEI will seek the guidance of the panel for the best targeted future research initiatives.

Advancing the Quality of Statistical Analysis

Underlying all of these questions is the continuing effort in the biostatistical community to advance the state of the art in statistical analysis, and the resulting challenges of ensuring that the new techniques are closely scrutinized, evaluated, and interpreted carefully. This includes new techniques for estimating exposure and testing exposure/health relationships, including emerging methods for causal inference. HEI has regularly delved deeply into these areas, funding both standalone efforts to develop and test new biostatistical techniques, and selecting, overseeing, and intensively reviewing new studies which seek to apply evolving techniques.

A related issue that underpins statistical analyses in the HEI-low exposure studies is how best to deal with “big data,” since these studies encompass tens of millions of subjects. Under such conditions, unexpected statistical issues can arise, such as an appearance of very high precision which may lead to overconfidence in the results. In activities we plan on advancing the quality of statistical analyses, we will also include a consideration of the “big data” issues.

Looking forward, this commitment to careful examination and evaluation of these techniques in specific studies will continue – at select times during the period of the new *Strategic Plan* HEI will need to identify whether special efforts – an expert panel, continuing statistical workshops, or other initiatives – will be needed to maintain the best possible application of statistics and interpretation of results.

Transport and Urban Health

There have been substantial improvements in vehicle emissions and transport-related air quality as requirements for cleaner fuels and technologies have been initiated and as transportation fleets are being replaced. These are having overall benefits even as the numbers of vehicles and travel activity grows. However, four factors contribute to continued attention to the role of transport in health:

- The growth in traffic activity around the world, and the persistence of older, less well-controlled vehicles in the fleet, have continued to focus both citizen and policy attention on traffic air pollution exposures. This has been amplified by recent awareness of the significant in-use exceedances of emission standards by many vehicles, especially in Europe. The past decade has also seen increased roadside monitoring of air pollution levels.
- Dramatic increase in waterborne freight and air travel have increased attention to the potential exposures and effects for populations living in and around sea- and air ports, populations which in many cases may be of lower socioeconomic status and facing increased underlying susceptibility.
- While the enhanced regulations and other activity worldwide to reduce vehicle greenhouse gas emissions is proceeding - resulting in substantial increases in the development and introduction of new “zero emission” technologies such as electric vehicles - the great majority of vehicles introduced over the next decade in response to these regulations are expected to continue to be internal combustion engines. These engines - primarily gasoline direct injection (GDI) - are substantially cleaner than older engines, but do, unless further controlled, have the potential for higher particle emissions than spark-ignition engines.
- Increasingly, recognizing the many urban factors that may contribute to population health, the evaluation of potential effects of traffic exposure has been broadened to examine a number of other factors that may also affect health, including noise, socioeconomic status, and access to green space.

At the same time, urban transport is going through potentially major and disruptive changes. A host of new mobility technologies (e.g. electric and autonomous vehicles) and transport services (e.g. transportation network companies such as Uber and Lyft) are being developed and implemented in cities in North America, Europe, and around the world. The exact trajectory of these changes is hard to predict, but depending on how the changes evolve, these could result in substantially reduced traffic congestion and air pollution, or in potential increases (as we have seen recently with the initial implementation of the TNCs resulting in increased vehicle travel).

These trends increase the need for targeted, advanced, and innovative exposure and health research to inform likely future questions on reducing such exposures and effects. They pose several major scientific challenges and opportunities for HEI to consider in constructing its *Strategic Plan 2020 – 2025*:

A First Step – the Updated HEI Traffic Review

Under the current Strategic Plan, HEI's new Expert Panel on the potential health effects of exposure to traffic is actively engaged in reviewing the literature published since HEI's earlier review in 2010. Since that time, over 1,000 studies of traffic exposure and health have been published. The new Panel is systematically screening and evaluating these studies, with an emphasis on studies of long-term effects. The Panel is endeavoring – in the face of this substantial number of new studies – to update our understanding of what we know about a variety of widely studied health effects and their potential relationship to traffic exposure. This effort, which is expected to be completed during the second year of the new *Strategic Plan* will enable a detailed review of whether some of the challenges identified in the 2010 report – such as the paucity of studies with high quality measurements of traffic exposure – have been addressed, and, importantly for HEI's *Strategic Plan 2020 – 2025*, should set the stage for the highest priority further studies to be tackled under HEI's new Plan.

Tracking the Advent of Major New Mobility Trends in Urban Transport

As noted above, even as vehicle technology is evolving to improve fuel efficiency and reduce GHG emissions using new versions of existing technologies, there are a host of new technologies and approaches being developed and implemented which could radically change the way transport occurs in urban areas around the globe. Even given the substantial uncertainties about the pace and ultimate form and magnitude of these changes, it will be critical for HEI to track these developments closely, identify and to the extent possible quantify likely trends, and anticipate at the earliest possible stage whether there are emerging issues relating to transport air quality and health that deserve HEI attention. This will include (a) tracking with our sponsors sales and other trends for new technologies, (b) assessing the evolving state of the art of modelling likely traffic and air quality implications of these technologies, and (c) identifying a small set of knowledgeable experts who we enlist as periodic advisors (likely in and around HEI's Annual Conference or a key meeting of the HEI Research Committee). This would be, initially, an assessment activity, with research to follow if key HEI-relevant questions should emerge.

Placing Transport Effects in Context of the Broader Range of Urban Health Factors

The HEI *Strategic Plan 2020 – 2025* will provide an opportunity to learn from HEI's newest studies of traffic, which were designed and implemented in the wake of a series of HEI studies to enhance the assessment of traffic exposure for use in epidemiologic studies (a key recommendation of HEI's earlier traffic review). These new studies, underway currently and likely to be reviewed and published near the middle of the new Strategic Plan, are incorporating improved traffic exposure approaches but also, importantly, considering other key factors found in the urban traffic environment that may also influence health. These factors include noise, socioeconomic status, and access to green space, for which there are separate literatures suggesting potential effects, that may modify or confound the effects of traffic air pollution exposure, and examining them all together should enhance our understanding of their roles in urban health.

Exposure Components of Special Interest

While traffic emissions have been dropping over the past several decades, some components of the traffic exposure mixture continue to call for and merit attention. They include:

- *Ultrafine particles*: HEI's 2013 Perspectives *Understanding the Health Effects of Ambient Ultrafine Particles* summarized current science on exposure to and health effects of ultrafine particles, and concluded "The current evidence does not support a conclusion that exposures to UFPs alone can account in substantial ways for the adverse effects that have been associated with other ambient pollutants such as PM_{2.5}." A recent review conducted for the German

Umweltbundesamt (the German EPA) reached similar conclusions. These reviews also identified a number of continuing research needs – and questions continue to be raised about ultrafines potential role in effects observed in traffic exposure studies, especially because it seems likely that some new technologies being introduced in the market, such as gasoline direct injection (GDI), emit UFPs. This set of issues is likely to continue to be of importance as decision makers in the US and globally consider what if any action to take on particle number standards for light duty and heavy-duty vehicles in light of the European action in this area.

HEI Action: HEI recently published a research solicitation, RFA 19-1, inviting research that would advance exposure assessment for air pollution and health studies using low-cost sensors, mobile monitoring, tracking technologies, and other approaches. The studies would develop and apply novel approaches to improve long-term (months to years) exposure assessment of outdoor air pollutants whose levels vary greatly in space and time, including UFPs as well as NO₂, black carbon, and others). Studies funded under this request for applications will begin their work in mid-2020; HEI expects that these studies will be completed, reviewed and published by the end of this grant period.

- *Non-tailpipe Emissions:* With a significant reduction of tailpipe PM emissions from gasoline and diesel vehicles, interest in non-tailpipe emissions of motor vehicles is increasing, and there is interest in understanding how the non-tailpipe emissions could affect exposures and health of individuals living near major roads. This area has not been studied adequately but there is an increasing level of interest in it. Among the constituents in non-tailpipe PM emissions, transition metals, such as copper (Cu), iron (Fe), and zinc (Zn), are of toxicological interest, and there is also an interest in the contribution of non-tail pipe emissions to the atmospheric burden of microplastics.

Non-tailpipe PM emissions are formed from mechanical processes and may be categorized as those arising directly from abrasion of brakes and tires, those generated by abrasion of the road surface, and those resuspended from the road surface. Like tailpipe emissions, the concentration of non-tailpipe emissions near the road is influenced by meteorology, vehicle type, traffic composition and conditions, and local dispersion characteristics. An important feature that complicates exposure assessment of the non-tailpipe emissions is that various manufacturers of brakes and tires use different materials, but their composition is proprietary, and their formulations change frequently. Additionally, the composition of materials used to build roads, their wear, and the contribution of dust from surrounding areas is variable. Interactions among the different non-tailpipe sources make the identification of unique markers extremely challenging.

HEI Action: In view of these challenges, HEI plans to assess the current literature and state of knowledge regarding research approaches and priorities in this area; this may take the form of a detailed literature review or HEI may organize a workshop, like it has done in planning other RFAs. Our goal is to issue a research solicitation during the second year of this grant period.

- *Increased use of Low Carbon and Biofuels:* As one element of a transition to lower vehicle greenhouse gas emissions, efforts to increase use of low carbon fuels are continuing. While these fuels offer an opportunity for cleaner emissions, they may also introduce new chemical compounds into the fuel mixture and combustion process, with a wide variety of potential effects on emissions. HEI has continued to track these questions over the last Strategic Plan, with a major multi-party expert workshop convened in Chicago in 2016 and monitoring of the latest science.

HEI Action: Given HEI's longstanding attention to the implications for air quality and health of changing fuels and technologies, HEI will be carefully assessing these developments and identifying constructive ways that HEI experts could inform future decisions about these fuels.

All of these components of the traffic mixture continue to attract scientific and policy attention. HEI plans to continue to work with its Committees, sponsor experts, and other stakeholders to identify the highest priority questions for HEI to address through targeted workshops and, if the questions merit it, new research.

Global Health

HEI, through its core air pollution and health program, has long provided domestically and globally relevant science designed to inform decisions by government and industry sponsors, WHO, the EU and others about public health, technology and potential regulation. This science also adds to the substantial base of global scientific evidence that help inform regulatory decisions in developed countries that are then transferred to the developing world (e.g. EURO vehicle standards)

With supplemental support, HEI's future work in Asia, South Asia and beyond, will enable HEI to provide much needed science on effects in local populations that can also inform extrapolation to the substantial body of global scientific evidence. This potent combination of local and global science can help to inform decisions in parts of the world with some of the very highest levels of air pollution. To do this HEI will work in partnership with leading global research institutes, investigator teams and agencies (e.g. Tsinghua, Fudan, IIT Bombay, NASA, University of British Columbia, and others) employing cutting edge satellite data, multi-scale atmospheric models, ground-based monitoring, and the growing base of health studies in many countries, often in a capacity building relationship with local scientists. This approach, and HEI's careful communication to decisionmakers builds trust and fosters the reliance on high quality consistent science for local decisions.

Europe and the Developed World

In Europe and elsewhere in the developed world HEI's engagement reflects the established priorities laid out in the body of this draft Strategic Plan; this will result in the provision of targeted science relevant to the needs of core sponsors, including government and industry alike, as well as WHO, environmental organizations, DG Environment, national governments and other key European institutions

Among key areas of wide interest to be pursued in Europe as part of HEI's broader global efforts are:

- Studies of low-level effects of air pollution
- The health impacts of exposure to traffic related air pollution
- Studies of ultrafine particles, NO_x, Ozone and advanced technology internal combustion engines

These and related research areas will help inform consideration of European limit values, emission ceilings, vehicle, and national and city level decisions about traffic control and related interventions. In turn, these decisions will provide guidance to many countries in the developing world who regularly adopt EURO vehicle standards and WHO limit values and guidelines.

Developing Asia and Beyond

As reported in State of Global Air 2019, in low- and middle-income countries, including East Asia and South Asia, air pollution and associated mortality and morbidity continue to increase, with over 90% of the world's population living in regions that exceed the WHO's most stringent health-based guideline. At the same time, as reported in GBD-MAPS, accelerating economic development will result in a number of changes that can act to increase emissions, including increases in electric power generation, vehicle ownership and miles traveled, and industrial activity. While growth will bring many benefits in improved socio-economic status, and declines in household solid fuel use, low and middle-income nations will be challenged to reduce air pollution and associated CO₂ emissions in the near term. In this context credible local science to understand the health impact of air pollution and specifically key sources will be important to help guide health-relevant interventions in nations with limited resources.

To respond to these and other challenges HEI will, with continued supplemental funding, to focus on several key areas:

Global Burden of Disease: HEI will continue to work with IHME, providing leadership on the air pollution working group to annually update health and monitoring data, including the addition of new studies and satellite and ground level monitoring, refine methods to estimate exposure response, and evaluate and add new health endpoints and pollutants for inclusion in GBD 2020 and beyond (e.g. birth outcomes, asthma, NO₂).

GBD-MAPS Global: The identification of contributing sources of air pollution and their relative health impact is vital to effective national air quality management. HEI will build on its successful GBD MAPS China and India studies, by using state of the art global emissions inventories by country and sector, combined with advanced modeling and updated integrated exposure response functions to build *GBD-MAPS Global*, a major report on source-specific air pollution health impacts for all of the countries in the world. As in China and India, this data is expected to aid health-based air quality management (e.g. key sources, fuel choices) in countries with limited ability to acquire this information on their own (e.g. South Asia and Africa). GBD-MAPS Global will also provide a comprehensive global analysis of key sources, effects and trends across regions and individual countries. This will also enable, over time, the projection and tracking of source impacts as populations and economies grow and evolve, (e.g. shifts in main power sources, and expected growth in vehicle fleets).

State of Global Air: HEI will maintain and enhance its flagship State of Global Air (SoGA) Report and database. SoGA 2020 and beyond will enable continued identification and tracking of key progress and trends in national, regional and global air pollution, beginning in 1990 through the current year. SoGA will report levels of PM_{2.5}, and ozone, and the health impacts of ambient and household air pollution, including measures of life expectancy. It will also provide an accessible and transparent mechanism for tracking progress in improving air quality. Beginning in 2020 SoGA and continuing in future years, will:

- report on the addition of new health outcomes
- enhance the ability to track Ozone and other pollutants
- report and synthesize evidence on progress in reducing air pollution and observed health benefits

SoGA will publish new periodic "interim reports" focusing on air pollution and health in specific regions and populations

New Research in a Capacity Building Framework: While there is a rich global literature on the health impacts of air pollution, there is growing recognition that, especially in some low and middle income countries, a subset of key studies are needed to credibly identify effects in local populations and inform extrapolation to the global literature. In addition, there is a dearth of studies of chronic exposures in Asian populations at high exposure levels that would be informative in refining estimates of health impacts in these same populations (e.g. in the Integrated Exposure response (or IER) curve used in the GBD). Under its new Plan, HEI plans to complete, peer review and publish the Asian air pollution cohort studies being undertaken by Vermeulen et al and identify and report on key science gaps and opportunities in that may exist in Asian cohorts. HEI will seek to support studies to fill those gaps, pursuing a capacity building model designed to enhance both the skills of local scientists to conduct such research in the future and produce results with maximum credibility to local officials.

Cross-Cutting Issues

In reviewing these detailed major opportunities that HEI might address going forward, a number of specific health effects questions were identified that would not by themselves be programs of research in the new Strategic Plan, but which should be viewed as *cross-cutting issues* that will be integrated into all of HEI's work. Several such issues are included above in discussion of specific research areas; they are also pertinent for future research throughout this Strategic Plan :

Transparency in Policy-Relevant Science

Many practices and other aspects of generating scientific information, particularly for its applications to policy making, have come under close scrutiny in the recent past. There are several elements in this complex debate. First, environmental policies are health-based and there have been long-standing debates about replicability and reproducibility of the studies underpinning regulations (including issues such as data access, quality, and analyses); additionally, reproducibility of the broader scientific literature is the focus of recent debates in scientific journals and also is reflected in the US government's attention to transparency. Second, the methods and procedures, and the potential for introduction of biases in drawing of conclusions from the scientific literature – in some cases, very vast literature – has been a subject of concern. Several guidelines and protocols have recently been developed, although their application has varied, partially due to the inherent features of observational epidemiology studies. Finally, recent years have also witnessed a growing interest in the application of statistical modeling methods to systematically explore causal relationships between air pollution and health; a variety of different methods have been developed, but the field is evolving and there are differing perspectives on how best to infer causality.

HEI does not plan to engage in research solely targeted at these issues but rather to integrate these considerations into all of HEI's research and review activities; we envision engaging in the following ways.

Data Access and Transparency are essential to the scientific process because they can provide insight into analytical and methodological details. Making data and analytical methods available allows others to replicate study results independently and, where necessary, perform alternative or additional analyses. Transparency is also valuable to the decision-making process by demonstrating robustness of reported findings.

Throughout its history, HEI has had a commitment to transparency and data access and maintains a strong policy on facilitating access to underlying data and methods for the studies it funds. In the past, 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, or their suitability for use in risk assessment. However, data for residential addresses and health outcomes in many cases cannot be made freely accessible to protect participants' privacy, limiting the ability to strictly replicate results.

During Strategic Plan 2020-2025, HEI plans to continue its emphasis in this area, by making data from studies it funds widely available for reanalysis, replication, and extended analysis by others. Specifically, as discussed above under Accomplishments, HEI will work with the investigators of the low-level exposure and its other studies to make their data and codes available. Details of HEI's policies in this area are provided as part of the HEI Quality Management Plan (See IV. h).

Systematic Synthesis of Information on Important Issues. Using special expert panels and its scientific committees, HEI has long played an important role in collecting, analyzing, and synthesizing scientific information on important issues facing the EPA and its private sector sponsors. This has taken the form of special reports and perspectives developed by special expert panels and staff. The most recent examples of such activities include a major review of the traffic literature (2010), ultrafine particles (2013), diesel epidemiology studies among miners and truckers (2015) and new technology diesel engines (2017).

The process for performing and synthesizing reviews has been evolving and currently the use of *systematic* review protocols has been emphasized in the environmental health context. However, it is also becoming clear that such protocols – often derived from clinical trials literature – are not well suited for the observational epidemiology literature. The HEI panel reviewing the health effects from exposure to traffic related air pollution has adapted procedures for its review work. The Panel's protocol was published in summer 2019 at the HEI website (<https://www.healtheffects.org/system/files/TrafficReviewProtocol.pdf>).

During Strategic Plan 2020-2025, HEI will finish and disseminate this traffic systematic review, and convene periodic workshops/meetings of experts in systematic review from multiple fields (e.g. at each HEI Annual Conference) to identify and help implement enhanced principles learned throughout its work going forward to advance the state of such reviews.

Testing and Evaluating Statistical Methods. HEI's work to develop statistical and analytical methods is most often integrated into other HEI research, an approach that we find enhances the effectiveness to the testing of the techniques, and speeds their adoption throughout science. In these areas HEI has played two key roles: to *develop innovative methods*, and then to *test and validate those methods* to ensure that they provide high-quality information for better understanding and decision making. Looking forward, there are several key opportunities for incorporating innovation and validation in all aspects of HEI's work, including

- *Testing Causality through Innovative Statistical Techniques* is a particular focus of research in HEI's currently funded study in the Medicare population under the low levels of exposure program. Specifically, those investigators are developing causal inference methods for spatio-temporal data that can be applied to the entire U.S., which is a highly complex endeavor. HEI will be looking for opportunities to fund other approaches to causal modeling under its accountability program.
- *Other Enhanced statistical techniques:* In its new Plan, HEI will continue its 15+ years of success at identifying, developing, and validating innovative statistical techniques for analyzing the relation between air pollution and health. After funding several studies to develop novel statistical methods to address the multipollutant mixture in the past, there will be continuing opportunities for HEI investigators to fine-tune those and other methods and apply them to existing datasets and new research data alike.

Enhanced Exposure Assessment

A primary challenge in conducting health effects research is ensuring the highest quality assessment of exposure for the population being studied. To that end, HEI works to address exposure issues in every study it funds, and both the HEI Research and Review Committees include experts who work to oversee the exposure assessment in each study – and then to review it rigorously once the work is complete. Even as those individual studies take place, HEI is always looking for ways to improve the techniques for exposure assessment for application in future studies.

HEI has new research just beginning under a new Strategic Plan, and is considering additional areas where HEI might engage during the course of the Plan:

- First, as discussed above, HEI has recently issued an RFA (19-1) seeking to fund studies to advance exposure assessment for air pollution and health studies using sensors, mobile monitoring, tracking technologies, and other approaches. The studies would develop and apply novel approaches to improve long-term (months to years) exposure assessment of outdoor air pollutants whose levels vary greatly in space and time, such as UFPs, NO₂, and components of PM, with particular attention to methods that may be applied to future health studies.
- Second, although HEI's current low-level studies are applying new satellite and chemical transport model techniques to estimate exposures, HEI will be closely following developments in this rapidly developing field and, as needed, identify specific efforts it might undertake to evaluate and enhance these techniques. In this context, HEI is paying particularly close attention to availability of data during the second half of this plan period on the sizes, compositions and quantities of particulate matter in air pollution from NASA's Multi-Angle Imager for Aerosols (MAIA) satellite.
- Third, as noted under Transport and Health above, there are a number of components of the transport exposure mix which continue to attract attention for their potential shorter-term exposures and effects. HEI will continue to monitor these issues and identify roles that HEI might play in improving assessment of these exposures.

Sensitive and at-Risk Populations

Laws to improve air quality, in the US, Europe, and elsewhere, frequently call for protection of sensitive or susceptible populations. Based on previous health studies, it appears clear that certain groups in the population are, or may be, particularly sensitive to health effects of air pollution. Such groups include the fetus and children who are in active developmental stages; the elderly who may suffer from multiple illnesses; those with asthma, diabetes, obesity, cardiovascular, and other diseases whose underlying pathophysiology makes them more vulnerable; and those who are of lower SES and may, due to economic, racial, and other factors, face higher exposures and have greater underlying health conditions. Also, in some situations, specific gene-environment interactions, including epigenetic factors, may confer susceptibility to individuals or groups. HEI will integrate such cross-cutting issues into its future research.