



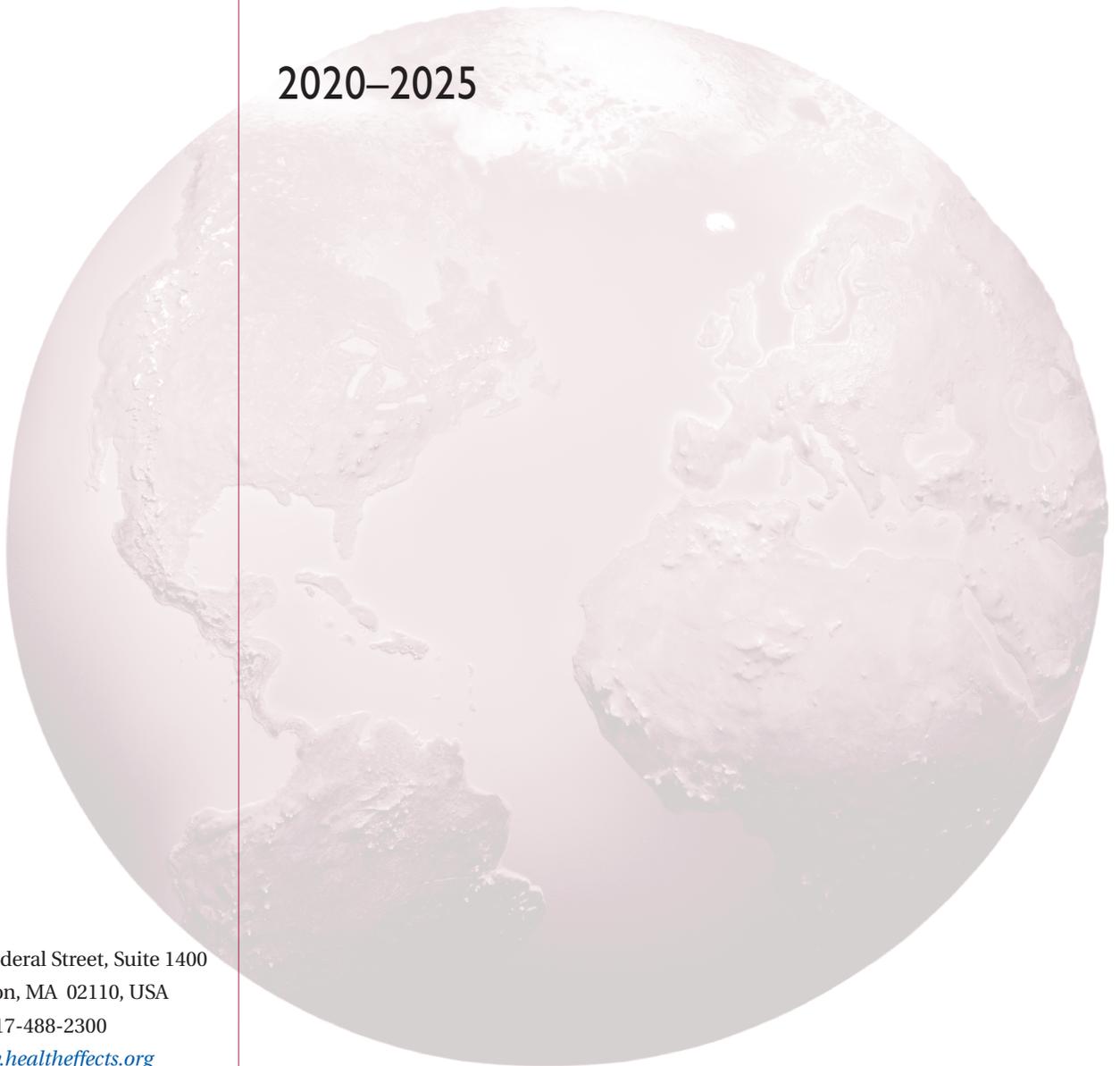
HEALTH
EFFECTS
INSTITUTE

March 2020

HEI STRATEGIC PLAN
FOR UNDERSTANDING THE HEALTH
EFFECTS OF AIR POLLUTION

2020–2025

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HEI Strategic Plan for
Understanding the
Health Effects of Air Pollution
2020–2025

Health Effects Institute
Boston, Massachusetts

Trusted Science • Cleaner Air • Better Health

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ABOUT HEI

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

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

HEI typically receives balanced funding from the U.S. Environmental Protection Agency and the worldwide motor vehicle industry. Frequently, other public and private organizations in the United States and around the world also support major projects or research programs. HEI has funded more than 340 research projects in North America, Europe, Asia, and Latin America, the results of which have informed decisions regarding carbon monoxide, air toxics, nitrogen oxides, diesel exhaust, ozone, particulate matter, and other pollutants. These results have appeared in more than 260 comprehensive reports published by HEI, as well as in more than 2,500 articles in the peer-reviewed literature.

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

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

HEI Strategic Plan for Understanding the Health Effects of Air Pollution 2020–2025

INTRODUCTION AND SUMMARY

The Health Effects Institute (HEI*) is entering its 40th year of working in unique partnership with the U.S. Environmental Protection Agency (EPA) and industry to provide independent, high-quality science on the health effects of air pollution. Since its founding, HEI has funded, through a leveraged partnership, over 340 strategic and targeted research projects, and published the results of over 260 of those studies, in addition to numerous other important special reports and reviews.

We are pleased to have made significant progress under the *HEI Strategic Plan for Understanding the Health Effects of Air Pollution 2015–2020*. In implementing the 2015–2020 Plan, we have initiated, conducted, and/or completed over 60 scientific studies and reports, including major studies on health effects of exposure to very low levels of air pollution and new accountability and traffic-related air pollution studies, to name just a few areas. We have communicated our results throughout the United States, and in capitals of Europe and Asia. Each of our published reports — and their accompanying journal articles — have been cited in the scientific literature an average of 129 times by other scientists, and our work was cited extensively in key decision documents from the U.S. Environmental Protection Agency, the World Health Organization (WHO), the International Agency for Research on Cancer (IARC), and many more organizations.

HEI's success at producing trusted science to inform key decisions relies on our ability to craft this Strategic Plan every five years to review what we have accomplished, anticipate the policy and science challenges ahead, and map out the most effective way for HEI to contribute to better decisions on air quality and health. Importantly, the quality of the HEI Strategic Plan depends on our ability to receive input from a wide variety of our audiences — our sponsors in government and industry; the scientific community; environmental and industry stakeholders; and international, national, state, and local agencies — to ensure that this Plan targets the most important topics.

The HEI Strategic Plan 2020–2025. In our consultations, we heard one key message: while we should, of course, plan for specific actions to undertake in the next five years, we should do so with a clear eye on the much longer time frames for future air quality and climate decisions. Challenging questions concerning air quality standards decisions continue to arise around the globe as the science evolves. Decisions regarding technology to meet air quality and greenhouse gas (GHG) goals (e.g., for vehicles and stationary sources) are likely to continue for many years beyond the time frame of this Plan. Given that, the HEI Strategic Plan is built around one overarching theme: *informing air quality and health decisions for 2020–2025... and beyond.*

HEI sees this theme integrated into four core program elements: accountability (testing the links between air quality actions and health); complex questions for the air pollution mixture; transport and urban health; and, with additional financial support, global health. In addition, we have identified a major cross-cutting issue, transparency in policy-relevant science, as well as other issues that we will integrate into all of our work. Those major opportunities are described in the section “The Major Research Opportunities” later in this Plan and are summarized here:

- ***Accountability: Testing the Links Between Air Quality Action and Health.*** This element of the Plan builds on HEI's accountability studies to assess the results of key actions to improve air quality by exploring questions such as whether there are better methods for testing links between such actions and any health benefits, whether accountability research helps us test for causality, and how such research might help improve cost and benefit analyses for future actions. Studies soon to be initiated under a recent Request for Applications (RFA 18-1) will address some of these questions, but, given the complex nature of this issue, more research is clearly needed. In particular, we will target studies that 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

* A list of abbreviations and other terms appears at the end of this volume.

makers alike. HEI's studies examining health effects at low-exposure concentrations are testing concentration–response relationships at the lowest levels, and, as a result of our recent RFA (19-1), the new studies on exposure will use sensors and other modern techniques to measure exposure to pollutants exhibiting a great deal of spatial and temporal variability (e.g., nitrogen oxides [NO_x] and ultrafine particles [UFPs]).

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 revisit particulate matter (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 developments are changing the future of transportation, even as the internal combustion engine will be used for many years and as issues from significant in-use exceedances of vehicle emission standards, seaport and airport emissions, non-tailpipe emissions, and other types of emissions continue to arise. In this context there are new questions, such as the health effects of exposure to UFPs, 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 challenges. With additional funding, HEI will continue and enhance its world-leading efforts to produce and communicate the results of the Global Burden of Disease from outdoor air pollution. HEI studies will shed light on the health effects of air pollution in developing countries, as well as produce a global analysis of the contributions to air pollution burdens from each source for every country in the world (Global Burden of Disease from Major Air Pollution Sources [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 and which we will need to integrate into everything HEI undertakes. Most

prominent among these 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 has maintained a strong policy on facilitating access to underlying data and methods for the studies it funds; during the Strategic Plan 2020–2025, HEI will strengthen its policies and efforts in this area.
- The processes for performing and synthesizing *systematic review of the scientific literature* have been evolving, and currently the use of *systematic review* protocols is strongly emphasized in the environmental health context. HEI is refining and implementing these enhanced processes in its reviews of the traffic literature and will target ways to further improve these practices in 2020–2025.
- *Testing and evaluating statistical methods* have been hallmarks of HEI's implementation of all of its research programs. These efforts will continue in 2020–2025, with particular emphasis on integrating new methods for causal inference and other enhanced statistical techniques into HEI research and evaluating their effectiveness; these novel approaches will pose opportunities and potential challenges.

While the *HEI Strategic Plan* is designed to be a clear path forward for us 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 also build in the flexibility to *anticipate and act on the unanticipated*, and fully expect to continue to have that capacity in the coming years.

HEI'S MISSION, GOALS, AND STRUCTURE

The Health Effects Institute is an independent, non-profit corporation chartered to “conduct . . . and to evaluate research and testing relating to the health effects of emissions from motor vehicles, and . . . other environmental pollutants, and to provide the results . . . to the public and interested governmental agencies.” Since 1980, HEI has provided high-quality science on the health effects of a broad range of mobile source and other air pollutants.

This Strategic Plan describes the potential HEI research program and review activities for the health effects of air pollution for the period of 2020 through 2025. We have attempted to identify and anticipate major questions on the health effects of pollutants and new technologies that are likely to be facing policy makers, industry, and others. Based on input from HEI stakeholders, the Plan presents an integrated set of strategies designed to guide HEI in developing detailed annual research and review plans that will deliver research results on the potential health effects of greatest concern for decisions in a timely manner.

HEI's mission is to provide public and private decision makers with independent, impartial, timely, and high-quality science on the health effects of emissions from motor vehicles, fuels, and other sources of environmental pollution. HEI accomplishes its mission by seeking to achieve six principal goals:

1. **To identify the areas of highest priority for health effects research** on pollutants and issues of greatest concern and that are responsive to the rapidly changing public and technological environment.
2. **To fund and oversee the conduct of high-quality research** in the priority areas, fostering whenever possible integrated and multi-institute efforts.
3. **To conduct, as needed, intensive reanalyses** of studies, datasets, and methods that are at the center of important policy decisions.
4. **To provide independent review of HEI-supported research and reanalysis** that evaluates, summarizes, and enhances the understanding and credibility of the results.
5. **To integrate HEI's research results with those of other institutions into coherent broader evaluations** of the health effects of a pollutant, source, or technology.
6. **To communicate the results of HEI research and analyses** to public and private decision makers and the scientific community in an understandable and timely manner.

CONSTITUENTS

HEI's success depends on cooperation, coordination, and communication among its many constituents. These include HEI's sponsors, the scientific community from which we draw investigators, Research and Review Committee members, expert panel members and reviewers, and a broad range of external stakeholders across all levels of government, environmental public interests, other industries, and nongovernmental organizations.

HEI's Board of Directors, President, and senior staff consult periodically with the sponsors, consider and respond to their diverse priorities, and then set the goals of the Institute and oversee its work. The Board, President, and senior staff also take into consideration the views of others in the public and private sectors who have an interest in environmental and health issues and who are important audiences for the results of HEI's work. Without broad stakeholder acceptance of the quality and independence of HEI's work, the effectiveness and impact of the Institute would be reduced.

HEI's sponsors provide recommendations to HEI about research priorities on the basis of their projections of research needs associated with regulatory activities, changes in the use of technologies and fuels, and new scientific information that raises concerns. In addition, HEI encourages scientists and others in government, industry, and environmental and health organizations to provide input about priorities for HEI research and to participate in its activities. HEI believes that the contributions of diverse sponsors and other stakeholders both in the United States and internationally will result in a Strategic Plan that is comprehensive, broadly relevant, and stands the best chance of accurately anticipating the emerging questions of science and regulation.

The HEI Research and Review Committees select, oversee, and evaluate the scientific activities of the Institute. The committees are multidisciplinary in nature and are composed of distinguished scientists who are knowledgeable about scientific issues related to study of the health effects of air pollution. The Research Committee and the Institute's scientific staff develop and oversee HEI's research program. The Review Committee, which has no role in selecting or overseeing the studies, works with other scientific staff members to evaluate and interpret each study. At each stage, Committee members who might have a conflict in reviewing either an application or a final report recuse themselves from all such deliberations according to well-established procedures. (See Table 1 for a more detailed description of the research and review processes.)

The Institute's scientific staff is highly qualified and actively engaged in all scientific activities. Other Institute staff provide expertise in administration, finance, and scientific publishing. The scientists at universities and research organizations who carry out HEI's selected studies are essential to the quality of HEI's research program and its broad content and diverse approaches. HEI, through the use of highly competitive national and international selection processes, has attracted an expanding community of scientists who develop new collaborations and fresh approaches

Table 1. HEI Research and Review Processes

RESEARCH PROCESS

Research Program Development

- Solicit sponsors’ views.
- Develop information on new research areas.
- Assess ongoing research by other institutions.
- Identify critical research needs.
- Develop Requests for Applications to meet specific research objectives and distribute to scientific community.

Project Selection

- Ad hoc panel of experts reviews and scores applications.
- Research Committee evaluates the top-ranked applications for relevance to HEI objectives and contribution to a coherent research program.
- Research Committee recommends studies for funding to the Board of Directors.
- Board approves evaluation process and studies selected.
- Research Committee requests study modifications as needed (for example, eliminating aspects of low interest or changing exposure concentrations).

Project Oversight

- Science staff organizes workshops to encourage interaction and collaboration among investigators conducting related new studies.
- Research Committee reviews progress reports; science staff communicates recommendations to investigators.
- Investigators present results and interact with HEI community at HEI annual conference.
- Research Committee and other experts conduct site visits at investigators’ institutions.
- HEI applies rigorous quality assurance program for studies with potential regulatory significance.

Final Report

- HEI requires a comprehensive final report at the end of each study.

Special Attributes of the Research Process

- HEI funds extramural research that draws on strengths of the scientific community and conducts a broad range of studies.
- Oversight methods encourage formation of coordinated program, with communication and collaboration among investigators.

REVIEW PROCESS

Objectives

- Provide critical and impartial evaluation of HEI-funded research.
- Ensure credibility of research findings.
- Place results into scientific and regulatory context.
- Identify future research opportunities.

Process

- External peer reviewers evaluate investigator’s final report.
- Review Committee considers external expert comments, evaluates report, and recommends revisions.
- Investigator submits revised final report.
- Review Committee and science staff develop Commentary, which critiques study and interprets findings.

- Editorial staff prepares report for publication.
- Review Committee approves Commentary; Board approves process.
- HEI publishes Research Report on website and in print.

Special Attributes of Review Process

- Review Committee conducts an in-depth external and internal review.
- Review Committee functions independently from Research Committee, which selected and monitored research.
- Results of all HEI-funded work, both positive and negative, are made available to the public.
- Review Committee prepares a Commentary on the research and results.

to the problems of air pollution and public health. Ultimately, the public, whose health is to be protected by standards and decisions based in part on studies funded and reviewed by HEI, is perhaps the most important constituent for HEI, its sponsors, and other stakeholders.

FUNDING

HEI typically receives balanced funding from the U.S. Environmental Protection Agency (EPA) and the worldwide motor vehicle industry. In addition, other public and private organizations in the United States and around the world support special projects or research programs. A complete list of current sponsors can be found at www.healtheffects.org/about/sponsors.

The HEI Strategic Plan for 2020–2025 offers substantial opportunities for building on the base of science created over the past five years. The Plan continues the work of applying targeted next-generation multipollutant approaches to important science and policy questions. In the context of increasingly complex questions about the effects of air pollution at lower and lower concentrations, HEI stands poised to make measurable progress in the areas of accountability; targeted exposure; epidemiology and toxicology; and transport and urban health.

Funds to Implement the Plan. HEI has had funding of \$5 million per year from U.S. EPA for the 2015–2020 years. This has been leveraged by an average of \$5 million per year from industry. HEI has also been able to further leverage EPA support by attracting additional resources beyond those provided by HEI's core sponsors. For example, *on the government side*, HEI has attracted modest new sponsorship for its traffic studies and other related efforts from the Federal Highway Administration (FHWA). *On the industry side*, HEI has attracted additional funding in the United States and Europe. Also, HEI's targeted international efforts in developing countries have attracted additional funds from other sponsors, particularly foundations.

Looking forward, funding — even maintained at current levels — presents a challenge, given continued inflationary erosion (with the value of research dollars down about 20% since 2015) and a substantial number of opportunities and needs identified by HEI's sponsors and others for the years ahead. In addition, HEI places a high priority — of great value to its sponsors — on maintaining enough flexibility in its planning and budgets to be able to adapt to and respond to unanticipated needs. Notably, the Institute has been successful — and expects to continue to be successful — in raising additional leveraged funds from other agencies and foundations, though such support has generally been for specific projects or programs.

PRIORITY RESEARCH AREAS 2015–2020

The *HEI Strategic Plan for Understanding the Health Effects of Air Pollution 2015–2020*, issued in April 2015, identified four major priority research areas: multipollutant science, accountability and transparency, emerging fuels and technologies, and global health science. In addition, HEI identified cross-cutting issues that apply across all research areas, including new statistical methods, susceptible populations, other health outcomes and modifying factors, mechanisms, and capacity building.

MULTIPOLLUTANT SCIENCE

HEI entered development of the last Strategic Plan in 2014 having completed several major studies on multipollutant exposures and health effects, including those focused on a better understanding of health effects from different PM components and sources (National Particle Component Toxicity Initiative [NPACT]), improved statistical methods, air pollution from traffic sources, and others. While the need for research on many of these topics continued, new scientific challenges were also identified during discussions of the new plan in 2014. Thus, Strategic Plan 2015–2020 focused on research on the effects of exposure to very low levels of air pollution, potential cardiovascular and respiratory effects of low levels of ozone exposure, exposures and health effects from traffic and port sources, and a new review of the literature on the health effects from exposure to traffic-related air pollution.

ACCOUNTABILITY AND TRANSPARENCY

HEI has historically played a leading role in accountability research, which examines the air quality and health impacts of actions to improve air quality. In the 2015–2020 Plan, the Institute further defined concepts and methods and initiated the next stage of research in this challenging field. Having completed a substantial body of research prior to 2015, HEI built on the lessons learned from those studies through critical review, publications, and collaborative efforts to identify and exploit new methods. Strategic Plan 2015–2020 posited completion of several ongoing studies, which extended opportunistic studies of shorter-term interventions to address larger regulatory programs implemented over longer periods of time. To accomplish this, the HEI program included research on enhanced analytical methods in the 2015–2020 Plan and also extended its ongoing work on transparency and data access.

EMERGING TECHNOLOGIES AND FUELS

Since its inception, HEI has played a role in assessing new fuels and technologies. With the introduction of a variety of new fuels and technologies, interest in such developments is high, especially given their implications for climate change, as well as conventional pollutant emission reductions. HEI's 2015–2020 Plan proposed several areas of evaluation and potential research, including examining the potential impact of the introduction of ethanol and gasoline direct injection fuels, potential increases in emissions of ultrafine particles, and non-tailpipe emissions (such as tire and brake wear).

GLOBAL HEALTH SCIENCE

In the 2015–2020 Plan, HEI built on key themes of accountability and multipollutant approaches through competitive selection of proposals from among the leading scientists in many countries of the world to fund research that informs decisions in North America, Europe, and Japan. The resulting HEI science is both domestically and globally relevant and has been regularly called on to credibly inform decisions affecting public health and potential regulation in key forums in the developed and developing worlds. With additional support from foundations and international sponsors, HEI selectively enhanced its research program in the developing economies of Asia, including in the areas of the Global Burden of Disease (GBD) from air pollution initiative, source specific health impacts, life expectancy, and examination of other long-term trends in worldwide air pollution and health.

MAJOR ACCOMPLISHMENTS 2015–2020

The past five years have seen substantial accomplishments for HEI in all areas of its Strategic Plan 2015–2020. These include a large number of research projects published, including major accountability studies, the comprehensive **Multicenter Ozone Study in OldEr Subjects (MOSES)** study examining potential cardiovascular effects in humans exposed to ozone, and a series of traffic exposure studies, among others. The Institute also saw the launch of major studies of the potential effects of low levels of exposure in the United States, Canada, and Europe; a new and updated review of the literature on traffic and health; and new studies examining traffic effects in the larger urban context. The following is a summary of those accomplishments. In addition, reports published in the past five years can be found at www.healtheffects.org/publications. Ongoing studies initiated between 2015–2020 can be found at www.healtheffects.org/research/ongoing-research.

MULTIPOLLUTANT SCIENCE

Estimating the Health Effects of Exposures to Low Levels of Air Pollution

Multipollutant Studies in Large Populations to Estimate Health Effects of Exposure at Low Concentrations. In the first years of the 2015–2020 Plan, HEI initiated a comprehensive program of three critical studies to characterize the potential health effects from long-term exposure to low levels of air pollutants. HEI undertook this program after a few epidemiological studies reported adverse health effects at levels even lower than the U.S. National Ambient Air Quality Standards (NAAQS). Following an expert/sponsor workshop in mid-2014 and publication of RFA 14-3, HEI decided to fund three studies, engaging highly qualified multidisciplinary investigator teams to examine air pollution and health relationships in very large cohorts in North America and Europe. The three studies are as follows:

- *Identifying the Shape of the Association Between Long-Term Exposure to Low Levels of Ambient Air Pollution and the Risk of Mortality: An Extension of the Canadian Census Health and Environment Cohort Using Innovative Data Linkage and Exposure Methodology* (Michael Brauer, University of British Columbia, Vancouver). This study is testing and extending analyses in Canadian cohorts where data on residential address and other confounders (smoking status, income, etc.) are available (total cohort size ~6 million).
- *Mortality and Morbidity Effects of Long-Term Exposure to Low-Level PM_{2.5}, Black Carbon, NO₂ and O₃: An Analysis of European Cohorts* (Bert Brunekreef, University of Utrecht, Netherlands). This study is conducting a pooled analysis in key populations from the European Study of Cohorts for Air Pollution Effects (ESCAPE) study, as well as companion analyses in six large administrative cohorts (total population size ~25 million).
- *Assessing Adverse Health Effects of Long-Term Exposure to Low Levels of Ambient Pollution* (including development of methods for causal modeling) (Francesca Dominici, Harvard T.H. Chan School of Public Health, Boston, Massachusetts). This study is conducting detailed and innovative analyses in the U.S. Medicare cohort (total population over 65 million), with additional analyses in the Medicaid cohort and the Medicare Current Beneficiary enrollees cohort.

The HEI program on the health effects of low levels of air pollutants has the following strengths:

- *Application of HEI's well-developed methods for study oversight*, with a special oversight panel and quality assurance/quality control audits performed by an independent contractor.
- *HEI's rigorous and in-depth review and evaluation*, including comprehensive comments, by an expert Review panel upon completion of the studies.
- *Very large populations*, with millions in the United States, Canada, and Europe, thus giving the studies an unprecedented statistical power.
- *State-of-the-art methods for exposure assessment*, at high spatial resolution (1 km² or residential address level) using satellite data, chemical transport models, land-use and weather variables, and monitoring data, for fine particulate matter (particulate matter $\leq 2.5 \mu\text{m}$ in aerodynamic diameter, or PM_{2.5}), ozone, NO₂, and — in some instances — PM components, such as BC and markers of non-tailpipe PM.
- *A wide range of mortality and morbidity health outcomes*, including all-cause and cause-specific mortality, lung cancer incidence, and cause-specific hospitalization.
- *Development and application of new statistical methods*, allowing for systematic, side-by-side comparisons with traditional analyses methods. Areas of refinement include methods to adjust for exposure measurement error, alternative ways to adjust for confounding and effect modification, and use of causal modeling techniques.
- *Opportunities to apply the same or similar methods for exposure assessment in different geographical areas*, for comparison among different approaches.
- *Highly experienced, multidisciplinary investigator teams* with extensive experience in cutting-edge research in exposure assessment, environmental epidemiology, and statistical analysis.

Each of the three studies is close to completion, and HEI anticipates final reports from these studies for review during the early part of the new Plan. After peer review and commentary preparation, we expect to publish these research reports in the first few years of the new Strategic Plan. HEI is working with the investigators of the low-level exposure studies to make their data and codes available.

While more detailed analyses are in progress, both the U.S. and Canadian teams have published early results from their work in peer-reviewed journals. Given the importance of these studies — both scientifically and in the context of public policy — HEI requested that two of the teams submit Phase 1 reports in 2019, comprising their analyses, results, and conclusions from the first two

years of the studies. HEI formed a multidisciplinary expert panel to review these Phase 1 reports and to prepare a Commentary discussing the research and the conclusions that may be drawn thus far (and which are expected to be further refined by continuing work). The investigators' Phase 1 reports and the Review Panel's Commentaries were published in late 2019 (HEI Research Reports 200 and 203).

Effects of Low Levels of Ozone on the Cardiovascular System.

Studies on the acute effects of ozone have largely focused on pulmonary effects — indeed, such effects are the basis for the current ozone NAAQS — and effects on the cardiovascular system have not received similar attention. Several epidemiological studies that included assessment of associations with specific causes of death have reported some associations of ambient exposures to ozone with cardiovascular mortality. In 2011, HEI initiated the **Multicenter Ozone Study in OldEr Subjects (MOSES)**, the largest and most rigorous study ever conducted, to investigate whether short-term exposure of older, healthy volunteers to near-ambient levels of ozone in a controlled exposure setting induces acute cardiovascular responses. The MOSES investigators tested 87 subjects at two levels of ozone (70 and 120 ppb) and clean air as control. The three investigators and their centers where the laboratory work was carried out were as follows:

- John Balmes, University of California, San Francisco, Medical School,
- Philip Bromberg, University of North Carolina Medical Center, Chapel Hill; and
- Mark Frampton, University of Rochester Medical School, New York.

In June 2017, HEI published a comprehensive report prepared by the multicenter team, which described the study and its findings in depth. HEI formed a special panel, which reviewed the report and its conclusions, and its commentary was published with the report. Additionally, HEI made provisions for full access to MOSES data to interested scientists and analysts; the data along with descriptive files are available from the Harvard Dataverse (<https://dataverse.harvard.edu/>). A small number of unused biological samples from the study were also made available.

In late 2017, HEI engaged the MOSES investigators to perform additional data analyses to examine whether any effects could be demonstrated from prior exposures (i.e., exposure during the hours and days before experimental exposures at the laboratory). The report from the latest analyses will be published in early 2020, along with the Panel's Commentary.

Examining Exposures and Health Effects from Traffic and Port Source Mixtures

Completion of Exposure Studies Previously Undertaken.

Despite significant progress in the control of tailpipe emissions from mobile sources and a general reduction in ambient air pollution levels, populations continue to live close to major roads and highways and are thus exposed to emissions from vehicle traffic that may have adverse effects on their health and well-being. In 2010, HEI published a comprehensive review of the literature on the health effects of traffic-related air pollution (Special Report 17). Among other research needs, the review identified a paucity of reliable information on human traffic exposure as a major gap in knowledge.

Initiating a research program on traffic-related air pollution, HEI funded new studies to improve exposure assessment to traffic-related air pollutants, as well as additional studies of non-tailpipe emissions (such as brake and tire wear) near roadways and of air pollution in tunnels. Three of the traffic studies have been published (led by Ben Barratt, Jeremy Sarnat, and Xiaoliang Wang), while two others (led by Stuart Batterman and Chris Frey) are in the midst of the review process. One study on non-tailpipe emissions (led by Meredith Franklin) is ongoing. Another study (led by Ying-Ying Meng), funded under HEI's accountability program, looked at the impact of air pollution regulatory programs in Southern California — an area whose air is heavily affected by port and goods movement activities — and has recently entered the HEI review process.

Launching a New Research Program Placing Transport in the Broader Urban Context.

Given the potential importance of traffic-related air pollution, as well as the increasing recognition that the effects of such exposures are also influenced by noise, socioeconomic status, and access to green space, HEI issued another RFA in 2017 to fund studies linking traffic exposure to health, including the impact of noise and socioeconomic status. HEI is now funding three additional studies (led by Payam Dadvand and Jordi Sunyer; Meredith Franklin; and Ole Raaschou-Nielsen). Work on each of these studies is underway.

Diesel Emissions and Health Effects. Early during the Strategic Plan 2015–2020, HEI published and widely disseminated two reports: HEI Special Report 19, *Diesel Emissions and Lung Cancer: An Evaluation of Recent Epidemiological Evidence for Quantitative Risk Assessment*, and the Executive Summary of the Advanced Collaborative Emissions Study (ACES). The first report was prepared by a special panel appointed by HEI to closely examine and evaluate the findings of the then-recent

studies of diesel emissions exposure and health effects in miners and truckers, each group exposed to emissions from old-technology diesel engines. The second report (ACES Executive Summary) was a comprehensive and succinct summary of an extensive HEI program whose goal was to characterize emissions from new-technology diesel engines, model-year 2007 and 2010, designed to meet the new stringent standards, and to test for health effects in an animal model. HEI presented — and continues to present — the findings of both reports at many major national and international meetings and symposia, as well as to governmental bodies.

Review of the State of Knowledge Regarding Health Effects of Traffic-Related Air Pollution.

Since publication of HEI's 2010 critical review of the literature on traffic-related air pollution and health, many additional studies have been published, and regulations and vehicular technology have advanced significantly. The topic continues to be of public health interest and is of concern to policy makers and motor vehicle manufacturers alike. During preparation of the 2015–2020 Strategic Plan, sponsors encouraged HEI to update the previous literature review. Therefore, in 2018 HEI formed a new panel of scientists with expertise in exposure assessment, epidemiology, and biostatistics. HEI charged them with the evaluation and synthesis of the evidence from the literature on associations of long-term exposure to traffic-related air pollution and the epidemiological evidence for selected health outcomes, keeping in perspective the influence of other factors such as noise, socioeconomic status, and green space. The panel is cochaired by Francesco Forastiere, (King's College London, UK) and Frederick Lurmann, (Sonoma Technology, Inc., Petaluma, CA)

HEI has also hired a team at the Swiss Tropical Institute to conduct the literature search. The Panel began its work in mid-2018 and has developed a protocol (available at www.healtheffects.org/system/files/TrafficReviewProtocol.pdf), risk-of-bias tool, and other instruments for its review; it has now begun literature searches and data extraction. Intensive work continued during 2019 and into the first part of 2020, with the report expected to be published, after peer review, in 2021.

Enhancing Exposure Assessment

Launching a New Research Program. Recognizing the challenges of accurately estimating exposures to a range of air pollutants whose exposure — especially long-term exposure — has been difficult to characterize, HEI recently issued RFA 19-1, titled *Applying Novel Approaches to Improve Long-Term Exposure Assessment of Outdoor Air*

Pollution for Health Studies. The RFA focused specifically on exposure assessment of outdoor air pollutants, whose levels vary greatly in space and time, such as NO_x, ozone, and UFPs. HEI received 41 preliminary applications in the summer of 2019, invited 10 full applications to compete for funding, and identified 5 studies to begin by mid-2020.

ACCOUNTABILITY AND TRANSPARENCY

HEI has continued its strong leadership in developing and funding innovative research on accountability during the 2015–2020 period.

Completion of Studies Previously Undertaken

Major accomplishments include the completion of four studies from the second wave of accountability (or health outcomes) studies, focused on examining the health effects of long-term actions to improve air quality at a regional and national level, assessing actions targeted at major ports, and improving statistical methods. Three reports were published (led by Zigler, Gilliland, and Russell); another study (led by Meng) of air quality improvements from regulation of goods movement in the Los Angeles/Long Beach area entered the HEI review process in late 2019, and publication is expected in 2020. In addition, HEI supported accountability-related research through other programmatic initiatives: A study to quantify the mortality benefits of transportation emission reductions in the United States and Canada by Amir Hakami was funded in the summer of 2018 through an open research solicitation.

Leadership Role in Developing Research in Accountability

In addition to funding research, HEI continued to lead in the scientific development of Accountability research by publishing three reviews, organizing conference symposia, and participating in research planning activities, among other actions.

Launching of Next-Generation Accountability Studies

In view of ongoing strong interest by sponsors and others in the scientific community, HEI issued RFA 18-1, *Assessing Improved Air Quality and Health from National, Regional, and Local Air Quality Actions*, to solicit a third wave of accountability studies. Twenty-eight preliminary applications were received in February 2019, and 10 applicants were invited to submit a full application. Four new studies were selected; they are expected to launch in early 2020.

Data Access and Transparency

Throughout its history, HEI has had a commitment to transparency and data access. HEI fosters transparency by encouraging researchers to make their data available to the public, as long as any data confidentiality agreements are not breached. Regularly, investigators are asked to share statistical code and other details of their analyses during the HEI review process for their studies. Recent examples of HEI-funded studies facilitating public access to data generated during research include the MOSES, Wang, and Dominici studies (Research Reports 192, 199, and 200, respectively). To date, the database for the MOSES study has been accessed over 150 times. For full details and a list of older studies, visit www.healtheffects.org/research/databases.

EMERGING FUELS AND TECHNOLOGIES

HEI has long provided critical information on key emerging questions relevant to motor vehicles and fuels, and HEI's goal is to continue to provide such time-sensitive information on the full range of emissions and effects of new technologies and fuels that are being driven by climate, energy efficiency, and air quality issues.

Regarding fuel composition and PM emissions, HEI organized a workshop in 2016, with the goal to present the latest information on the impact of ethanol and aromatics in fuel, the use of gasoline direct injection, and the challenges in meeting the latest U.S. and California standards. HEI published an Executive Summary of this workshop, which highlighted the salient scientific and policy-relevant findings of the presentations and discussions.

Ultrafine Particle Emissions. UFPs and their potential impact continue to be an area of interest, and measurement and effects of ultrafines are a part of several HEI studies. The abovementioned workshop on fuel composition and PM emissions also included useful information on UFP emissions. As discussed earlier, HEI recently issued RFA 19-1, titled *Applying Novel Approaches to Improve Long-Term Exposure Assessment of Outdoor Air Pollution for Health Studies*. The RFA is focused, among other pollutants, on ultrafine particles.

Non-Tailpipe Emissions. As the overall tailpipe emissions of PM decrease due to the use of diesel particulate filters and other technologies, more attention is being paid to non-combustion emissions of PM, for example, dust from brake and tire wear and resuspended road dust. Such emissions have not been well studied or characterized. HEI has funded two studies in this area and may undertake additional research in the future.

GLOBAL HEALTH SCIENCE

In the context of sustained interest and demand for HEI-funded science in the United States, HEI has worked systematically and carefully to extend the scope of its science to be globally relevant by obtaining added support from a range of philanthropic, government, industry, and banking sources. These additional resources enable HEI to support a broad portfolio of globally relevant science.

HEI's global program includes studies reported earlier in this plan that are directly relevant to research questions and decisions in the United States, Europe, and Japan — areas where complex mixtures of lower levels of many air pollutants, advanced technologies, accountability, traffic exposures, methods development, and causality are of primary concern. This work is often undertaken in partnership with or to inform decisions by WHO (e.g., the Global Air Quality Guidelines for major pollutants) and the European Commission (e.g., European Air Quality Limit Values) and to assess the effectiveness of traffic and other air quality actions and regulations.

For the developing world, added foundation funding from HEI's global program has supported a diverse program of air pollution science and communication: in Asia (with a focus on China and India), in parts of Eastern Europe, and in Africa, where air pollution levels and public health impacts from ambient and, in some regions, household sources are high and often increasing.

Taking a global perspective uniquely positions HEI to inform understanding of the health effects associated with air pollution across the full range of exposures and of the relative importance of different sources of air pollution and health impacts using local evidence. This scientific work has enabled HEI to inform regulatory decisions in highly polluted, highly populated areas in ways that not only provide air quality benefits to local populations, but also reduce transport of pollutants to Japan and North America. Our work on the air pollution from key sources and fuels and any health impacts also provides a health-based rationale for moderating greenhouse gas production in developed and developing countries.

Supporting Internationally Relevant Studies

As noted above, in the current plan HEI initiated or completed a range of studies that directly inform decisions in the United States, as well as in other countries, in priority research areas of multipollutant science, emerging technologies and fuels, and accountability. Representative examples include:

- The study described earlier of low-level effects of ambient air pollution and mortality in large cohorts by Bert Brunekreef and colleagues in Europe;
- A study by Xiaoliang Wang and colleagues evaluating how mobile-source emissions have changed by examining real-world emissions characterization in tunnels in Hong Kong and Baltimore, Maryland;
- A study that developed a dynamic three-dimensional land-use regression model for Hong Kong to estimate exposure to traffic-related air pollution at ground level and upper elevations of street canyons formed by high-rise buildings by Benjamin Barratt.

Results of these and companion studies have been and will continue to be actively communicated in the United States; at key European and globally relevant forums and scientific workshops, including at WHO, Directorate-General for the Environment (European Union), and IARC events; and to national governments as they consider evaluation of WHO Air Quality Guidelines and interim targets, European limit values, national emission ceilings, and standards for stationary, mobile, and other sources. The outcomes of these deliberations, in turn, provide important guidance to many developing countries as well.

Low- and Middle-Income Countries

In the developing world, especially in India, China, and elsewhere in Asia, rapid growth has raised the level of air pollution from all sources. However, the development of locally relevant scientific evidence critical to informing decisions is often lagging, limiting the ability to address this problem. HEI has raised significant additional funding from foundation and other sources to provide key science, capacity building, and communications in developing countries where levels of air pollution consistently exceed health-based international and national standards.

Key Results

Key results from HEI's global program include the following:

Support for the Global Burden of Disease. The GBD study, from the Institute for Health Metrics and Evaluation (IHME), which is updated annually, represents the most comprehensive and credible worldwide assessment of all major risk factors associated with death and disease. HEI and our partners (at the University of British Columbia and elsewhere) have provided leadership on the air pollution analysis for all GBD releases during the last Strategic Plan and worked with IHME and others to communicate air pollution's global and country-specific impacts to national policy makers and stakeholders.

GBD's 2017 report, published in *The Lancet*, relied on updated data and methods to identify air pollution as the fifth-highest-ranking risk factor for mortality worldwide, just behind measures of poor diet, blood pressure, tobacco use, and high blood sugar. For the first time, estimates of air pollution's impacts on mortality and disability included the contribution of diabetes; additional health outcomes are under consideration for inclusion in future updates.

Source-Specific Impacts of Air Pollution. The developing world faces significant limitations on emissions, air monitoring, and health data and, as a result, information on source-specific health impacts. Such information is key to educating the public and regulators about sources and enabling all to make informed choices about health-based air quality management, now and projecting into the future under business-as-usual and more aggressive scenarios. Over the past 5 years, HEI has brought together leading scientists and institutions from China (Tsinghua University) and India (IIT Bombay) with experts from Canada and the United States in its Global Burden of Disease from Major Air Pollution Sources (GBD MAPS) program. The program published the following reports:

- *Burden of Disease Attributable to Coal-Burning and Other Major Sources of Air Pollution in China* (August 2016), which identified emissions from industrial, energy, and domestic coal combustion as a significant contributor now and going forward, and
- *Burden of Disease Attributable to Major Air Pollution Sources in India* (January 2018), which identified residential biomass, anthropogenic dusts, and coal as emission sources with major health impacts.

State of Global Air. During the last 5-year strategic plan, with added funding, HEI conceived, published, and widely communicated a new flagship annual publication and website: *State of Global Air* (SoGA). SoGA is a unique resource that builds on the annual GBD results to report on the levels and burden of air pollution for every country in the world in a current, searchable database. SoGA provides data on levels and trends in air quality in each country and on health impacts attributable to air pollution (mortality and disability-adjusted life-years), offering the ability to track progress (or lack thereof) on a country-specific, regional, and global level.

SoGA was also designed to report on key studies beyond GBD, including results from WHO, the International Energy Agency, World Bank, and other analysts, to enhance understanding of differences and similarities in

methods and results worldwide by providing the results in a single location.

The SoGA report is updated each year to respond to changing data:

- *SoGA 2017* introduced data on the significant global mortality impact of air pollution worldwide and highlighted those regions that are most and least affected.
- *SoGA 2018* updated the above information and focused in depth on tracking trends in India and China, as well as on the significant burden of household air pollution.
- *SoGA 2019* provided new information on life expectancy and on diabetes as a newly documented health outcome, and signaled progress in China with initial declines in air pollution levels.

As with all HEI reports, results are communicated to national decision makers in partnership with leading local health and academic partners to help ensure credibility.

Building a Stronger Scientific Base. A recent example of HEI's efforts to build a stronger basis for understanding the effects of air pollution on health is our funding in 2017 of a major multicountry, multicity study in Asia led by Roel Vermeulen. Vermeulen and his colleagues are investigating the associations between residential air pollution and natural-cause and cause-specific mortality (including cardiorespiratory and lung cancer outcomes) by linking detailed estimates of residential ambient PM_{2.5} and NO₂ exposure to data for participants within several pre-existing and well-characterized population cohorts across Asia.

Evaluating HEI Global Science. HEI concluded the 2015–2020 period with a formal survey of a broad range of stakeholders who accessed SoGA 2019 or are prospective future users of SoGA results and data. The goal was to identify the extent to which SoGA reporting is relevant and useful for local needs, to assess user satisfaction, and to identify priorities for SoGA 2020 and beyond.

CROSS-CUTTING ISSUES

Many studies mentioned in the previous sections addressed cross-cutting issues, including advancing statistical methods, at-risk populations, other health outcomes and modifying factors, enhanced exposure assessment, mechanistic studies, and capacity building. Accomplishments during Strategic Plan 2015–2020 include the following:

- HEI funded studies to *advance statistical methods* to more accurately understand and interpret data from epidemiological studies (Molitor, Park, Zigler, Coull, and

Batterman). Additionally, under the HEI program on the health effects of exposure to low levels of air pollutants, several new methods are being developed, targeted at refinements to methods for exposure assessment and causal inference (Brauer and Dominici).

- Laws to improve air quality in many countries frequently call for protection of *sensitive populations*. HEI supported studies in this area including research in the young (Gilliland), pregnant women (Lee, Qian, and Wu), the elderly (MOSES), and individuals with asthma (Pedersen).
- *Enhanced exposure assessment* is a key component of many HEI studies (e.g., the studies on exposure to low-levels of air pollution and traffic), and HEI investigators conducted studies to develop and apply advanced techniques, using satellite data, chemical transport models, land-use and weather variables, and monitoring data, for state-of-the-art exposure assessment at wide geographical scales. HEI has also funded other research to improve exposure assessment and has just issued an RFA focused specifically on exposure assessment of outdoor air pollutants, such as NO_x and UFPs, whose levels vary greatly in space and time.
- HEI supported studies examining *other health outcomes and modifying factors*, including reproductive effects and pregnancy outcomes (studies led by Dadvand, Wu, Qian, and Molitor), neurocognitive outcomes (Chen), and autism (Guxens), as well as noise (Franklin and Raaschou-Nielsen) and socioeconomic factors (Clougherty and Raaschou-Nielsen).
- HEI funded studies focused on *mechanisms* that are important in forming and transforming air pollutants in the atmosphere (Surratt and Ng) or in producing toxicological effects (Contreras, Fryer, Gowdy, and Shiraiwa).
- HEI supported *capacity building*, by funding early-career investigators who focus their research on environmental health. Since 2015, HEI has funded six such investigators under its prestigious Walter A. Rosenblith New Investigator Award: Apte, Contreras, Gowdy, Guxens, Pedersen, and Shiraiwa.

MEASURING HEI'S IMPACT

IMPACT ON SCIENCE

HEI focuses its efforts to ensure that the science it produces is both relevant to decision makers and advances understanding across the scientific community. HEI is also strongly committed to tracking the Institute's progress in meeting these goals. HEI initiated and completed a large number of projects undertaken to implement the HEI

Strategic Plan 2015–2020. Beyond these activities, however, HEI regularly examines other measures to assess how effective HEI's work has been in informing both our scientific and policy audiences. The results of our review of these measures are summarized below.

Studies Started and Completed

As described in Table 2, HEI initiated 31 studies of air pollution health and exposure over the five years of the 2015–2020 Strategic Plan. HEI published 22 Research Reports, including several reports that were large, complex, and multipart (such as the MOSES report). HEI published 10 Communications and Special Reports, including publications focused on exposure to and health effects from diesel, source-specific burdens in China and India, and household air pollution in Ghana. Currently, HEI has 5 reports in its review and publication process (including MOSES Part 2 and an accountability study). HEI also maintains data from key studies at publicly accessible websites and, from time to time, other air pollution data.

Study Dissemination

HEI has a tradition of distributing scientific reports and summaries of those reports (referred to as “HEI Statements”) to a growing list of HEI sponsors, scientists, and interested parties in government, environmental organizations, and industry. Between 2015 and 2019, HEI distributed more than 2,000 Research Reports and nearly 12,000 HEI Statements. All HEI reports are also available online at www.healtheffects.org/publications. Our website — which was comprehensively redesigned in 2016 — has proved to be an increasingly effective means of extending HEI's reach. Website downloads may be the best measure of the value of HEI publications, because downloading is an active process undertaken by people who think a report may be of value. HEI has seen substantial and increasing distribution of its scientific documents online. Each year, the HEI website is visited by more than 35,000 visitors, who viewed more than 145,000 web pages and downloaded some 29,000 Research Reports, Special Reports, HEI Statements, and other documents. In addition, HEI's new State of Global Air website (www.stateofglobalair.org) attracted 15,000 visitors in its first year and 27,000 in the second year, with around 6,000 report and figure downloads in both years. At this writing, 2019 is showing similar trends.

Citation of HEI Reports in the Scientific Literature

Another measure of HEI's impact is the extent to which the scientific community reads and uses our scientific reports. HEI recently calculated how often our Research Reports and scientific papers resulting from HEI-supported

Table 2. Number of HEI Research Studies and Publications, April 2015–March 2020

Topic	Studies Initiated	Reports in Review	Reports Published*	Other Documents Published
Air Pollution Mixture				
Low-Exposure Epidemiology	3	0	2	0
PM, Ozone, and Other Gases	9	3	9	0
Traffic Exposure and Health	4	1	4	1
Non-Tailpipe Exposure	1	0	0	0
Enhanced Exposure	5	0	0	0
Innovative Statistics	0	0	3	0
Emerging Technologies	0	0	0	1
Accountability	2	1	3	0
Third Wave	4	0	0	0
International	3	0	1	8
TOTAL	31	5	22	10

* Excluding 5 unpublished reports.

work, published between April 2015 and March 2020, have been cited in the scientific literature. Results of this analysis suggest that HEI's impact is substantial (Figure 1).

- A total of 22 HEI Research Reports were published through Year Five of the Plan; these were cited 116 times in more than 50 health and atmospheric science journals. (Since some of those reports were published only recently, we would expect citations to rise in the coming years.)
- The work described in the 22 reports also resulted in 87 peer-reviewed scientific articles; these peer-reviewed publications, in turn, were cited 2,737 times in other publications.
- Thus, the 22 HEI-funded reports published between April 2015 and March 2020 generated an average of 130 citations per report (citations of the original report and

its related journal articles), an extraordinarily high number of citations for any scientific work. Note that these data do not include the 30 studies that are currently in progress and their publication in peer-reviewed journals, nor do they include HEI reports published before 2015, which continue to be cited.

IMPACT ON POLICY

The full measure of HEI's effectiveness must include some consideration of how well the science it produces is communicated and put to use in decision making. Similar to the citation counts in the scientific literature, how often HEI reports are cited in regulatory documents can help gauge our impact. By this measure, HEI has significantly contributed to the scientific basis of norms, standards, and guidelines in the United States and elsewhere.

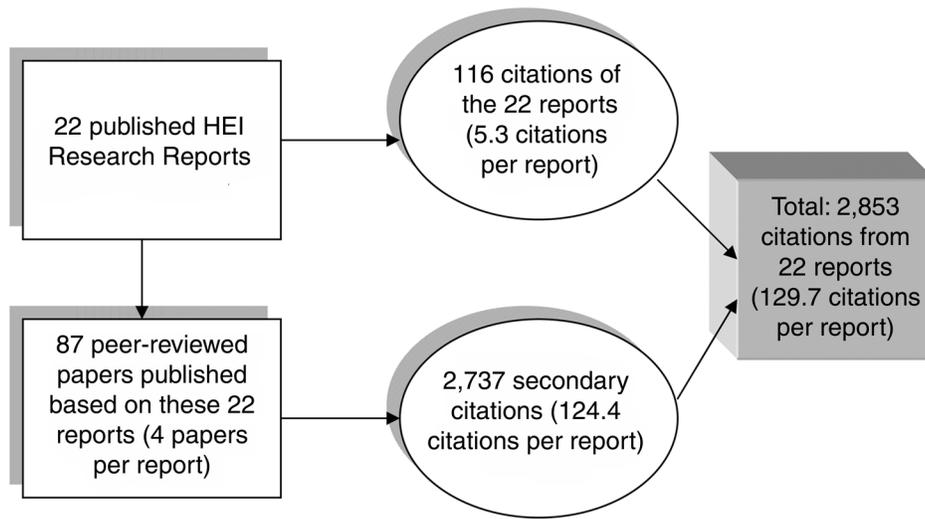


Figure 1. Citations of HEI Research Reports (published during 2015–2020) and accompanying journal articles in the scientific literature. (Numbers in parenthesis are average per report.)

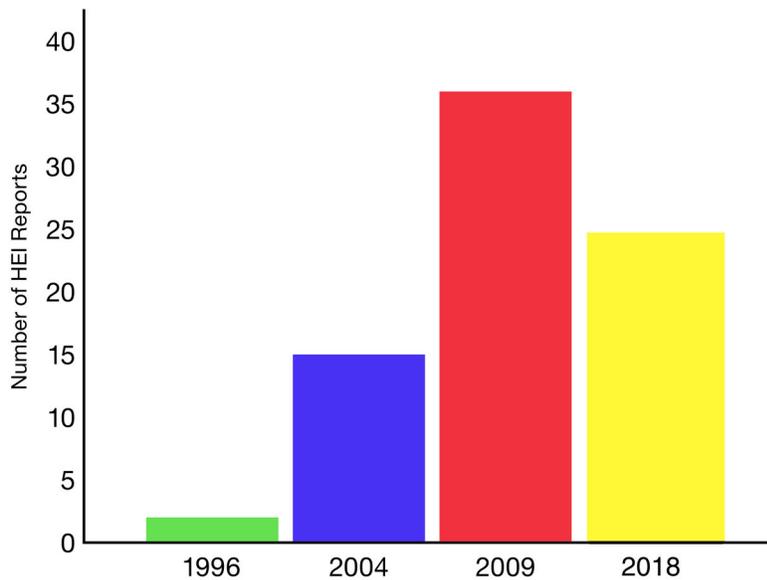


Figure 2. Citations of HEI reports in key U.S. EPA scientific summaries.

As one example of a public agency using HEI’s research, Figure 2 illustrates the degree to which U.S. EPA, in reviewing the broader literature, has cited a series of HEI reports in its last four reviews of the particulate matter ambient air quality standards. And this impact is likely significantly understated, as it includes only citations of HEI

reports themselves in the Integrated Science Assessments; as noted above, for each HEI report there are roughly 4 journal papers produced whose citations in the Integrated Science Assessments are not counted in Figure 2. Equally significant is the fact that HEI’s reports are also cited in the most recent assessments done for each of the other criteria pollutants.

Communication does not end, of course, with the citation of an HEI report in a regulatory document. HEI engages in frequent outreach to the leadership and staff of government and industry sponsors and is often invited to share its science and expertise with a wide set of other public and private actors shaping environmental and public health policy on air pollution. Since 2015, HEI has presented information, provided testimony, and offered technical advice and other assistance in many settings, for example:

- *U.S. governmental agencies and legislative bodies:* The U.S. Congress; Federal Highway Administration; National Institutes of Health; Occupational Safety and Health Administration; Department of Energy; and California Air Resources Board;
- *Public and private advisory bodies:* The National Academies of Science, Engineering and Medicine; and the EPA Clean Air Act Advisory Committee and Mobile Sources Technical Review Subcommittee;
- *International organizations and agencies of foreign governments:* The European Commission; European Parliament; World Health Organization; International Agency for Research on Cancer, World Bank; the UK Committee on the Medical Effects of Air Pollution; China Ministry of Ecology and Environment (including the annual Air Benefit and Cost and Attainment Assessment System [ABaCaS] meetings); and India Ministry of Environment, Forests and Climate Change; and
- *Private sector associations and public interest groups:* American Forest and Paper Association; American Lung Association; American Petroleum Institute; Conservation of Clean Air and Water in Europe (CONCAWE; research organization of the European oil industry); Auto Alliance; European Automobile Manufacturers Association (ACEA); Engine Manufacturers Association; Environmental Defense Fund; European, U.S., and Indian Emission Control Manufacturers; Natural Resources Defense Council; and Union of Concerned Scientists.

THE CHALLENGES AHEAD: THE POLICY AND SCIENCE CONTEXT

POLICY CHALLENGES

Identifying the highest priority needs and concerns of air pollution policy makers is a critical element in HEI's research planning. While it is clear that air quality goals remain a significant focus of public interest and heated debate in the United States and globally, new health concerns and an increasingly complex energy landscape are challenging established air pollution strategies and raising

new research priorities. This is apparent in a broad range of recent and ongoing regulatory reviews and other policy-setting activities that stress issues such as potential unaddressed human health impacts, even at very low pollutant concentrations; characterization of exposures in highly localized environments; and the health of children and other sensitive populations. In addition to further studies on specific questions, research agendas will be driven by the development of new scientific approaches and more powerful means of assembling, managing, and sharing data. Surrounding all are persistent calls for closer scrutiny of the scientific basis of regulatory decisions, the determination of causality, and the eventual outcomes of adopted measures. The following sections briefly outline some of the areas likely to be important over the next several years.

Continuing Questions About Ambient Air Quality Goals — Decisions Amid Both Increased Evidence and Further Uncertainties

The review of the latest science on PM_{2.5}, ozone, NO₂, and other pollutants — and the consideration of current and future ambient air quality standards — are continuing at a sustained pace in the United States, Europe, and globally:

- In the **United States**, the U.S. Environmental Protection Agency has recently completed the review of the U.S. NAAQS for NO₂ and is deep into the review of the science for the NAAQS for PM_{2.5} and ozone. The latter two reviews have a target for completion by the end of 2020, with implementation to follow throughout the 2020s.
- At the **World Health Organization**, the review of the Air Quality Guidelines is proceeding, with the planned completion and journal publication of systematic literature reviews for the major pollutants (i.e. PM_{2.5}, ozone, NO₂, CO, and some air toxics) to be published in 2020, and the completed reviews and establishment of guidelines likely to take place in 2021. While these guidelines do not directly affect U.S. standard-setting, U.S. EPA is an active participant, and the guidelines play a significant role in the setting of European Air Quality Limit Values as well as standards in many countries around the world (e.g., China has set their PM_{2.5} standard at a level [35 µg/m³] equivalent to the highest tier of the WHO Air Quality Guidelines). As a result, the guidelines are directly relevant to U.S. interests and to domestic and global industry.
- The **European Union** recently concluded a *Fitness Check* review of its entire Air Quality Limit Values setting and implementation program. That report has now been submitted to a new European Commission and European Parliament, and the Commission recently

issued its European Green Deal, committing to consider aligning the EU Limit Values better with the WHO Air Quality Guidelines — a process that is expected to get underway in 2020 and 2021 — among many actions.

There is growing awareness of air pollution issues in many of the world’s rapidly developing economies:

- **China** has escalated the pace and extent of the country’s efforts to improve air quality. A series of stringent emission control measures has resulted in the first documented significant reductions in ambient levels. Those levels, however, are still well above the China PM_{2.5} air quality standard; further work will be necessary and has been initiated.
- In **India**, growing awareness of the air quality problem has led to accelerated implementation of new vehicle standards by 2020, expanded use of liquefied petroleum gas for households, and the launch of the first-ever

National Clean Air Programme. Implementation efforts are now being developed.

- In both of these countries and around the developing world, there is a need for high-quality, targeted local science — especially on longer-term effects — to inform and provide the basis for the continuing and challenging air quality decisions.

The current NAAQS and WHO assessments highlight a number of uncertainties and limitations in understanding that are likely to be key areas for future reviews. Some reflect long-standing questions, while others have arisen more recently.

- With levels of PM declining across the United States (Figure 3) the question of whether a threshold level of effects from PM exposures exists or can be determined through epidemiological analysis is a persistent challenge that may gain new attention as studies reporting

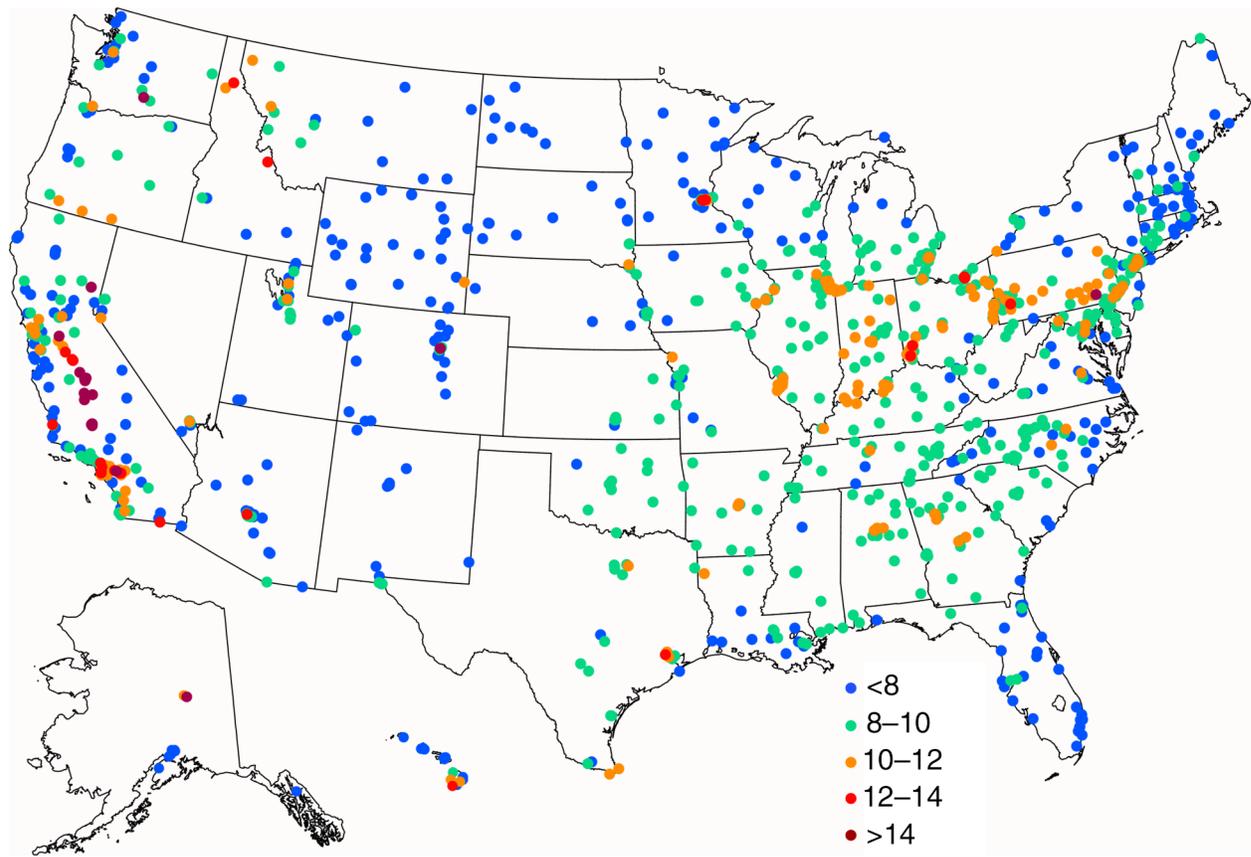


Figure 3. Three-year average PM_{2.5} concentrations (µg/m³) 2013–2015, showing a decline in PM. (Source: U.S. EPA PM Integrated Science Assessment, December 2019; Figure 2-13.)

associations at very low levels of ambient concentrations are conducted.

- At the same time, the advent of these questions and the publication of work on low-level associations have raised renewed questions about how to best determine the causal connections between exposures and effects, especially regarding other lines of evidence — from animal toxicology and human clinical studies — that are more difficult to conduct at such low levels. The current debates have also amplified the need for and implications of Accountability studies designed to test whether actions taken to reduce air pollution have actually reduced exposure and had health benefits.
- There has also been growing attention to exposures to and health effects from NO₂, with somewhat different patterns of regulatory and policy activity on both sides of the Atlantic.
 - In the United States, following an earlier review of the NAAQS for NO₂, a new network of roadside monitors was installed to monitor both NO₂ and PM_{2.5}. However, the finding of relatively low levels of NO₂ has led to a scaling back of those monitors for NO₂ and a decision to retain the current NAAQS, even while retaining the roadside monitors for PM_{2.5} (see Figure 4).
 - In contrast, in Europe, the higher levels of NO₂ at roadside (due in part to the higher proportion of earlier-model, less-well-controlled, light-duty diesel vehicles) — and a significantly more stringent Limit Value than the U.S. NAAQS — have resulted in many more locations facing the challenge of reducing NO₂ concentrations and exposure.
- Even as these trends in major pollutants and regulation continue, it is becoming increasingly apparent that a *changing climate* could have impacts on the levels of

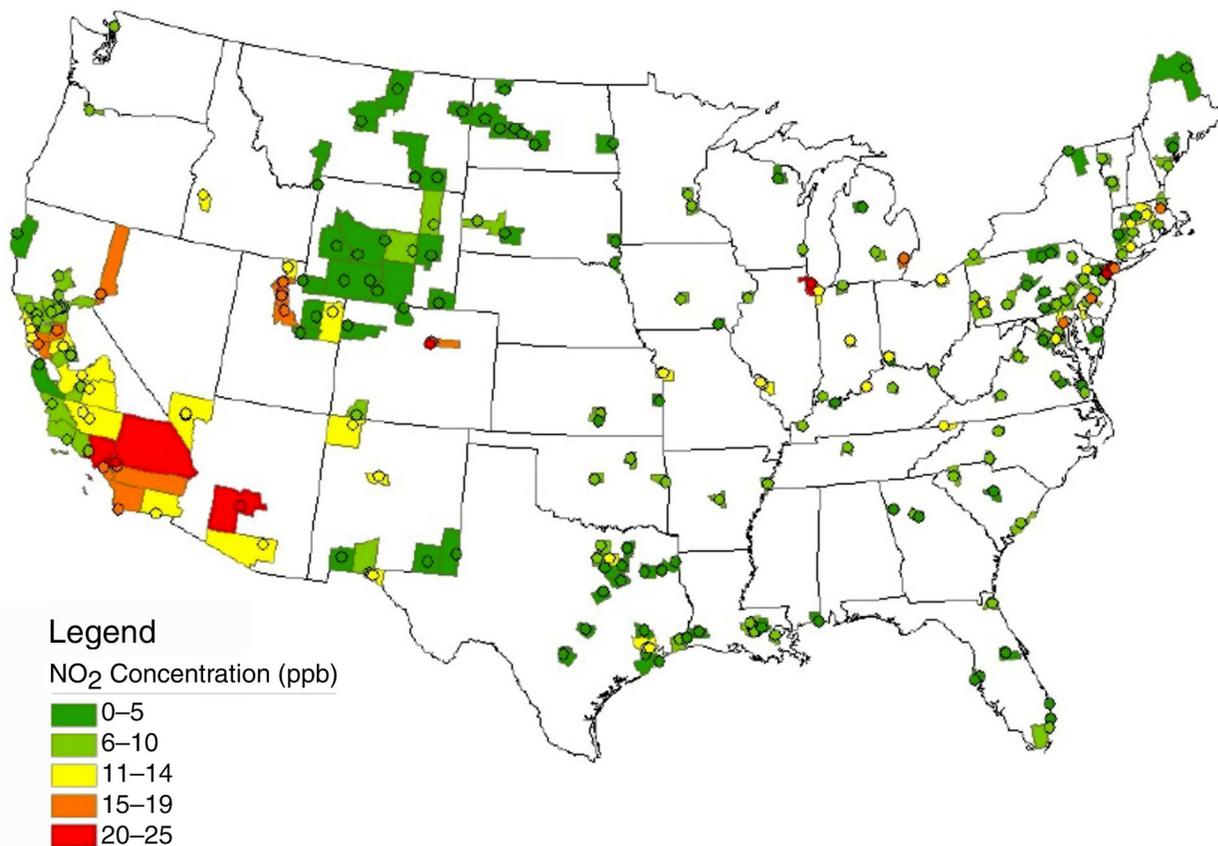


Figure 4. U.S. annual average NO₂ concentrations for 2013. (Source: U.S. EPA Integrated Science Assessment for Oxides of Nitrogen – Health Criteria, January 2016; Figure 2-12).

future pollutants. While the exact pace and magnitude of climate change are the subjects of active scientific investigation and modeling, there is growing evidence suggesting that, as the climate changes, those pollutants whose concentrations are strongly influenced by meteorology — especially ozone — may experience more frequent excursions and become more resistant to efforts to control emissions and effects.

Source Emissions — Transport and Energy Choices

Interest in mobile source air pollution emissions has continued to grow around the world and will likely continue to expand over the coming years — despite significant achievements in reducing vehicle emissions — as vehicle ownership and vehicle miles traveled (VMTs) grow. At the same time, new, potentially disruptive mobility technologies (e.g., electric and autonomous vehicles, and car sharing) are likely to begin to change the very nature of vehicle fleets and emissions. However, despite the significant progress in these new technologies, it is likely that the great majority of light-duty vehicles to be introduced over the next decade will continue to be enhanced-efficiency internal combustion engines, primarily employing gasoline direct injection technology.

The sustained growth in vehicle ownership and VMTs has led to continued attention to vehicle emissions standards in major markets around the world, including the implementation of Bharat Stage VI standards in India and in China, potential new additional NO_x controls in California and other states for heavy-duty vehicles, and the initial discussions about a new Euro VII in the coming decade. This recent wave of regulation is attempting to address a range of issues:

- *Continued air quality concerns*, particularly around ozone and the role of vehicle NO_x emissions in the persistence of continued high ozone levels in some regions, remain. This has been the case in southern California, where the challenges of ozone attainment are seen as calling for significant new actions, in part to address concerns that diesel emission control technologies may not yield the expected NO_x reductions mandated by the 2010 rules. U.S. EPA has now begun to propose revising the national standards for NO_x emissions.
- Highly visible cases in both Europe and the United States of problems with *actual in-use emissions far exceeding standards* are leading to far-reaching efforts to control real driving emissions (RDE) in Europe and to strengthen in-use enforcement in the United States.
- *Rapid transitions in engine technologies and fuels*, pursued for fuel efficiency and GHG reductions, directly

bear on emission control considerations in various ways. Some emerging technologies have raised questions about changes in the composition and pattern of emissions, especially in the potential for increased UFP emissions from direct injection engines. These concerns played a role in the development of a particle number standard for both diesel and gasoline vehicles in Europe and continue to be raised elsewhere in a number of policy and regulatory discussions.

- There is a *continuing and growing focus on reducing emissions from existing fleets*, including actions such as funding retrofit and replacement of “high-emitters” and implementing new U.S. roadside monitors (see Figure 5), which are likely to focus increased attention on PM exposures, even as NO₂ exposures have been found to be lower than expected.
- With the advent of low-cost sensors, the *availability of widespread information on air pollution levels* — though of uncertain quality — is likely to result in increasing pressure to control such community and neighborhood emissions.

Emphasis on Regulatory Effectiveness and Transparency

With the advent of increasingly stringent rules at lower levels of air pollution, there has been growing attention to the effectiveness of regulations, the transparency of rule-making, and the ownership and control of the data underpinning scientific research in ways that are particularly relevant for air pollution decision-making.

- A key challenge involves *demonstrating the benefits that accrue from efforts to reduce emissions*. The need to hold regulations accountable (i.e., to better understand and measure the outcomes of air quality interventions) continues to be a high priority among policy makers, who seek both a better grasp of the costs relative to the benefits of risk management decisions and a more robust way of evaluating the likely impact of alternative approaches. However, the direct demonstration of such benefits remains challenging in many situations because of the overlapping nature of regulatory program implementation and concurrent, unrelated changes — such as in the economy, employment, and healthcare — which may also affect health.
- Equally important are longstanding debates over how to best ensure that the scientific evidence relied on in regulatory processes is properly developed and interpreted in the most *transparent* manner possible. The challenge of satisfying demands for greater transparency heightens the value of sound models of data reanalysis and evaluation.

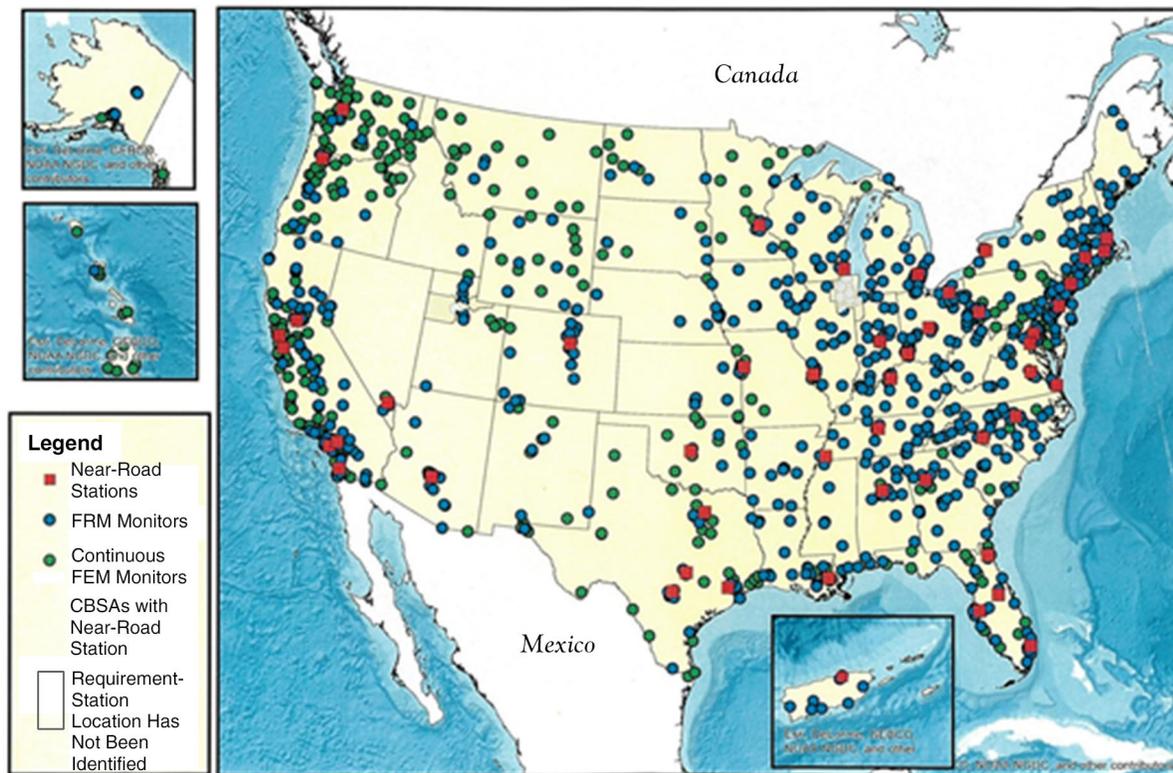


Figure 5. PM_{2.5} network, including near-road monitors. (Source: U.S. EPA PM Integrated Science Assessment, December 2019; Figure 2-10.) (CBSA = core-based statistical areas; FEM = Federal Equivalence Method; FRM = Federal Reference Method.)

- These issues also apply increasingly to enhancing the transparency and quality of any *systematic review* of scientific literature, including establishing a priori protocols and identifying the tools to be applied to find publications and to evaluate them for quality and risk of bias.
- *Facilitating public access* to federally funded research was established as a policy objective by the U.S. government in 2013, and federal agencies have been engaged in a coordinated effort to develop and implement access plans. While the scope of concerns is wide and touches on fundamental aspects of the scientific enterprise, questions such as how to best enable innovative approaches to previously unexploited sources of information, from often dispersed and enormous datasets collected for disparate purposes, directly bear on how future air pollution health research will be designed and practiced.

SCIENCE CHALLENGES

Finding the best scientific approaches for assessing exposures to and health effects from air pollutants continues to pose significant challenges. The following are the highlights of some major challenges. Later, in the “Major Research Opportunities” section, we discuss how HEI plans to approach them.

- *Assessment of health effects of exposure to low levels of pollutants.* As we discussed earlier, evidence is emerging that, even at and below the ambient NAAQS standards for PM and ozone, associations of adverse health effects with air pollution exposure are being observed. If these observations are confirmed by additional, well-designed analyses, they will be of great interest to scientists and policy makers alike. However, very large populations and air quality exposure assessments are needed for such studies, and development of methods for ensuring the best possible control for confounders in these large populations remains challenging.

- Further, the emergence of these results from large-population-based studies poses a *challenge to animal toxicology and human controlled-exposure studies*, where small numbers of animals and subjects and high costs make assessing biological effects at low levels very difficult.
- *Access to and analysis of information in large populations.* Perhaps the best source of health data in large populations comes from census and healthcare utilization organizations (health insurance companies or federal programs). However, access to and analyses of such administrative data are complicated by confidentiality and privacy considerations ensured under federal and state policies. These populations also pose analytic challenges, both because they may not contain extensive information on relevant personal confounders that may independently cause or modify effects and because the sheer size of the datasets can present computational challenges, even in this era of advanced supercomputers, along with novel questions about statistical interpretation.
- *Development of new methods for testing and determining causality.* HEI and other scientific institutions have been investing in developing and applying new statistical techniques — causal inference statistical models — to attempt to determine the nature of the association between exposure and effect. These models are still in various stages of development but offer a potentially valuable complement to traditional weight-of-evidence techniques.
- *Availability of reliable data on population exposure.* The reliance on central-site monitoring data alone for health studies has well-recognized limitations. Although there have been improvements in exposure modeling (e.g., land-use regression), there are now several emerging trends in attempts to improve exposure assessment. These include:
 - *Microscale exposure assessment*, which takes advantage of new *low-cost sensors* to greatly expand intensive exposure measurement. These techniques can enhance coverage of and variability within populations. They come, however, with the challenge of ensuring the quality of such measurements. These sensors are also increasingly being used in “citizen science,” resulting in greater democratization of accessibility to the data, but also increased challenges regarding both data quality and the understanding and communication of the potential risk.
 - Increased reliance on *satellite imaging* and *hybrid modeling* for estimating PM concentrations — and

increasingly for other pollutants — in order to maximize the populations and areas available for analysis. This approach, however, continues to be evaluated, and questions about exposure measurement errors persist.

- *The challenge and opportunity of “big data”.* In analyzing both the health status and exposure of large populations, innovative new methods — including some employing uncommon approaches such as “citizen science” and exploitation of large datasets that are becoming available through large-scale, networked populations (i.e., so-called big data) — may offer opportunities to analyze exposure and effects with much greater refinement, although many conceptual and analytical issues need to be addressed to ensure that the results are valid.
- *Development of methods for assessing the toxicity of ambient air pollutants.* Although numerous methods to assess the mechanisms of toxicity, such as genotoxicity, oxidative stress, and mitochondrial damage, are being used, their protocols have not been standardized, making it difficult to compare studies from different laboratories. There is also a recent trend in applying methods developed by molecular biologists — such as genomics, proteomics, and other “-omics” — to environmental health problems. Although several groups are applying these new methods, there is a need to develop the methods further, to standardize their protocols, and to assess their ability to predict effects in humans.

CHOOSING THE FUTURE

HEI has considered a spectrum of air pollution and health issues, as well as many other broader concerns, in developing its 2020–2025 Strategic Plan. A draft Plan for discussion was distributed to participants — including the various sponsor groups and scientific committees — at HEI’s Annual Conference in May 2019 for comments and suggestions. Figure 6 presents the topics discussed in that draft Plan, the process for evaluating them, and the priority topics in this final Strategic Plan. As shown, the draft Plan laid out broad opportunities, as well as many narrower topics, related to concerns about specific pollutants. The Plan was discussed with representatives from HEI’s EPA and motor vehicle industry sponsors, from the oil and other industries, and from the scientific, regulatory, and environmental communities.

HEI received much valuable input during these discussions and also received written comments. In considering this input carefully, HEI staff and committee members

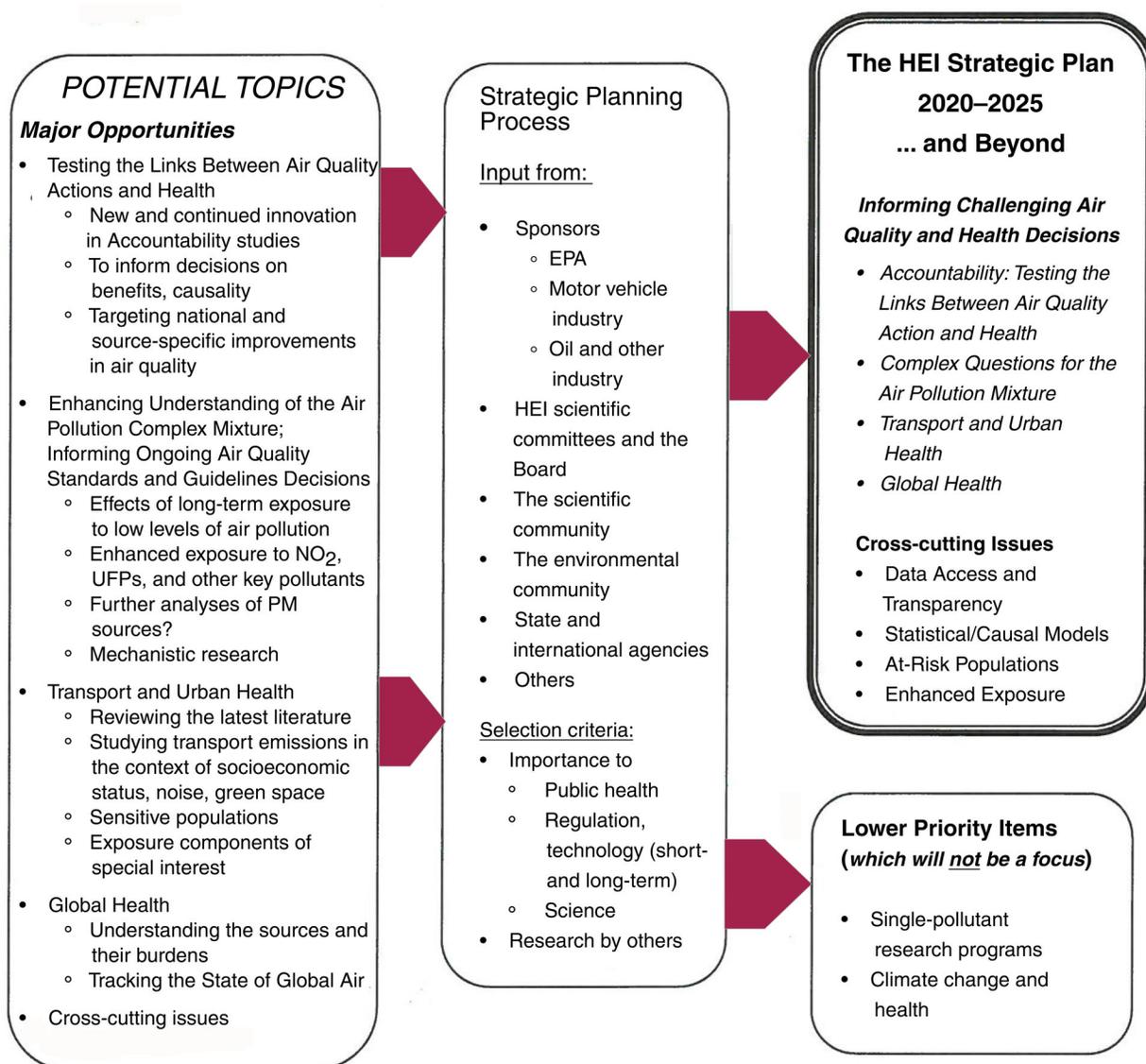


Figure 6. Choosing the future. Steps in selecting priority topics for HEI's Strategic Plan 2020–2025.

addressed several criteria in selecting priority topics for the next five years:

- the current state of knowledge about topics of potential interest,
- their importance for public health and upcoming regulatory and technology decisions,
- how well they are being addressed by other organizations, and
- the likelihood that scientific work by HEI will produce useful findings within the foreseeable future.

WHAT WILL HEI'S STRATEGIC PLAN FOR 2020–2025 ADDRESS?

One key theme we heard in comments on the draft Plan was that, while HEI must of necessity plan for specific actions to be taken in the next five years, the Institute should do that *with a clear eye on the much longer time frames for future air quality and climate decisions*. Challenging questions surrounding air quality standards decisions continue to arise around the globe as the science evolves, and the technology to meet GHG goals (e.g., for

vehicles and stationary sources) continues to change, raising issues beyond the scope of this Plan. Given that, the HEI Strategic Plan is built around one overarching theme, discussed below.

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

Moving forward, HEI is integrating this longer time frame into four core program elements and one major cross-cutting theme:

- *Accountability: Testing the Links Between Air Quality Action and Health.* This element of the Plan builds on HEI's accountability studies, assessing the outcome of key actions to improve air quality by exploring questions such as whether there are better methods for testing links between such actions and any health effects, whether accountability research helps us test for causality, and how such research might help improve cost and benefit analyses for future actions. Studies soon to be initiated under a recent Request for Applications (RFA 18-1) will address some of these questions, but given the complex nature of this issue, more research is clearly needed. In particular, we will target studies that 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 recent RFA on exposure (19-1) will seek out studies using sensors and many other new techniques to measure exposure to hard-to-characterize pollutants (e.g., NO_x and UFPs).

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 revisit 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 developments are changing the future of transportation, even as the internal combustion engine will be used for many years and as issues from significant in-use exceedances of vehicle emission standards, seaport and airport emissions, non-tailpipe emissions, and other types of emissions continue to arise. Other questions are emerging in this context, such as the

health effects of exposure to UFPs, 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 in 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 the Global Burden of Disease from outdoor air pollution initiative. HEI will improve the science on the health effects of air pollution in developing countries, as well as produce 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 and which we will need to integrate into everything HEI undertakes. Most prominent among these 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 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 continue to be a very important feature of research sponsored under the HEI Strategic Plan 2020–2025.
 - The process for performing and synthesizing *systematic review of the scientific literature* has been evolving, and currently the use of *systematic review* protocols is emphasized in the environmental health context. HEI is implementing these enhanced efforts in its review of the traffic literature and will target ways to further leverage these practices in 2020–2025.
 - *Testing and evaluating statistical methods* have been hallmarks of HEI's implementation of all of its research programs. These efforts will continue in 2020–2025, with particular emphasis on integrating new methods for causal inference and other

enhanced statistical techniques into HEI research and evaluating their effectiveness; these novel approaches will pose opportunities and potential challenges.

We also expect to pursue other cross-cutting issues in our research, including a focus on 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 because of their socioeconomic status) and on *enhanced exposure assessment; new biological 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 also 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, the approaches that HEI will take in addressing them (“Major Research Opportunities”), and the timetable for implementation (“Implementing the Strategic Plan 2020–2025”).

What Will HEI’s 2020–2025 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 *not* to 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 will focus instead on multi-pollutant 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).

MAJOR RESEARCH OPPORTUNITIES

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

- Accountability: Testing the Links Between Air Quality and Health

- Complex Questions for the Air Pollution Mixture
- Transport and Urban Health
- Global Health

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 stem in large measure from the importance of assessing whether complex policies and actions, and other interventions, actually yield 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 (*Assessing the Health Impact of Air Quality Regulations: Concepts and Methods for Accountability Research*, September 2003). Since then, HEI has funded two successful waves of studies that evaluated both local interventions occurring over relatively short periods of time and 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 2020. RFA 18-1 identified the following areas as high priority for further research: studies that evaluate policies and actions at the national or regional level implemented over multiple years; studies that examine 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 next five years, 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, HEI is beginning a new program of research — with four new studies funded under RFA 18-1 being launched in early 2020 (led by Adar, Harper-Baumgartner, Hystad, and Kinney) — to set the stage for the next generation of

accountability studies 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 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 is 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 to 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 United States, 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 has reviewed and selected several new studies of major interventions at different geographical scales; these 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, for example, congestion charging and low emission zones, limited driving days for cars with certain license plate numbers, road closures or restricted access to certain streets (e.g., Oxford Street in London), or outright bans of certain vehicles (e.g., diesel vehicles). These actions go hand in hand with efforts to transform urban mobility. These new developments lead to growing attention to 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 HEI's newly funded studies are evaluations of local and state traffic interventions and old-technology diesel bus replacement, and their implications for air quality and health.

HEI is also continuing to solicit timely accountability study ideas through a newly released open RFA (20-1) and plans to continue such solicitations in the future.

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% 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 employing 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 part of a systematic, multidisciplinary program that 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 definitively 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 in the source and composition contributions to the toxicity of

PM remains high. Interest in other characteristics of PM, particularly size, also continues to be high.

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

Health Impacts 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 to air pollutants, applying innovative exposure and analysis techniques to examine 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, including 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 methodological advances in air pollution studies for years to come.

Testing the Robustness of Findings. As the first step after the completion and intensive peer review of the low-exposure studies by a special HEI Review Panel, HEI will fund a modest effort to test whether their findings are reproducible using different statistical approaches. The three HEI-funded low-level studies have used somewhat different methods for their exposure assessment, evaluation of health outcomes, and statistical analyses, raising the question of whether their results will be robust to analyses using alternative methods. HEI believes that the three 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, multipollutant analyses, measurement error, confounder adjustment, causal inference, and dose–response modeling.

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, and the HEI 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 with either one of HEI's existing committees or a new separate panel, HEI will prepare and publish such a synthesis within the time frame of this Strategic Plan.

Asking a Key Question: Where Can Science Best Contribute?

In the past decades, the science on the health effects of exposure to air pollution has made great strides. Scientific studies using epidemiological, clinical, toxicological, and mechanistic research have provided valuable information, forming the basis for policy actions and 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 health effects in epidemiology analyses in low-exposure studies raises questions concerning the biological/toxicological mechanisms that may operate under chronic, low-exposure conditions. Though toxicological and mechanistic confirmation of effects is not essential for evaluating epidemiological observations, such information can contribute to assessment of the broader weight of evidence for plausibility and causality, as has been the case noted 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 answers to these questions are not straightforward, and the insights of the special panel should provide valuable guidance to ensure that HEI makes the most effective research investments in this important area.

Characteristics and Toxicity of PM Components. Another important issue where insights from the special panel would be very useful stems from the continued intense interest — and potential policy decision value — in whether any specific characteristics 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 and surface charge, the nature of PM (e.g., freshly emitted PM, secondary organic aerosols, and aged PM), and many other attributes that 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 biostatistics 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 effort 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, both funding standalone efforts to develop and test new biostatistical techniques, and selecting, overseeing, and intensively reviewing new studies that 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. Among activities under consideration to advance the quality of statistical analyses, HEI will also include the “big data” issues.

Looking forward, HEI’s commitment to careful examination and evaluation of statistical 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 — for example, 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 requirements are providing overall benefits even as the total numbers of vehicles and travel activity grow. However, four factors have contributed to continued attention to the role of transport in health:

- *The growth in traffic activity around the world and the persistence of older vehicles in the fleet with less well-controlled emissions* have continued to focus both citizen and policy attention on traffic-related air pollution

exposures. This has been amplified by a recent awareness of the significant in-use exceedances of emission standards by many diesel vehicles, especially in Europe. The past decade has also seen increased roadside monitoring of air pollution levels.

- *Dramatic increases in waterborne freight and air travel* have increased attention to the potential exposures and effects for populations living in and around sea- and airports — populations that in many cases may be of lower socioeconomic status and facing increased underlying susceptibility.
- While the enhanced regulations and other activities worldwide to reduce vehicle GHG emissions are proceeding — resulting in substantial increases in the development and introduction of new “zero emission” technologies such as electric vehicles — *most 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 more efficient than older engines but — unless their emissions are strongly controlled — do have the potential for higher particle emissions than the traditional spark-ignition engines.
- Increasingly, in recognition that *many urban factors such as housing quality, economic inequality, and other characteristics 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, they 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 transportation network companies, 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 Panel on the Health Effects of Long-Term Exposure to Traffic-Related Air Pollution 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 further studies of the highest priority 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 that 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 air quality and health issues relating to transport 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 modeling likely traffic and air quality implications of these technologies, and (c) identifying a small set of knowledgeable experts whom we enlist as periodic advisors (likely meeting in and around HEI's Annual Conference or at 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 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 epidemiological research (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 period, are incorporating improved traffic exposure approaches. They are also, importantly, considering other key factors found in the urban traffic environment that may also influence health, including noise, socioeconomic status, and access to green space, for which there are studies suggesting potential impacts. These factors may modify or confound the effects of traffic-related air pollution exposure, and examining them all together should enhance our understanding of their roles in urban health. These studies can, in turn, set the stage for HEI to take a next step — depending on their findings — into exploring the much broader socioeconomic context in which urban health is shaped.

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 publication *Understanding the Health Effects of Ambient Ultrafine Particles* (HEI Perspectives 3) summarized current science on exposure to and health effects of UFPs and concluded that “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 Environment Agency) reached similar conclusions. These reviews also identified a number of continuing research needs, and questions continue to be raised about UFPs' 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 GDI, emit UFPs. This set of issues is likely to continue to be of importance as decision makers in the United States 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: Under RFA 19-1, HEI recently reviewed and selected new studies for research that will advance exposure assessment for air pollution and health studies using low-cost sensors, mobile monitoring, tracking technologies, and other approaches. The studies — being led by de Hoogh, Hoek, Katsouyanni, Sheppard,

and Weichenthal — will 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 work in mid-2020; HEI expects that these studies will be completed, reviewed, and published by the end of this Strategic Plan 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 the exposures and health of individuals living near major roads. This area has not been studied adequately. Among the constituents in non-tailpipe PM emissions, transition metals (such as copper, iron, and zinc) are of toxicological interest, and there is also an interest in the contribution of non-tailpipe emissions to the atmospheric burden of microplastics.

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, as it has done in planning other RFAs. Our goal is to issue a research solicitation during the second year of this Strategic Plan.

- *Increased Use of Low Carbon and Biofuels:* As one element of a transition to lower vehicle GHG 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 period, with a major multiparty expert workshop convened in Chicago in 2016, and has continued monitoring of the latest science in subsequent years.

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 helps inform regulatory decisions in developed countries, which can then be transferred to the developing world (e.g., EURO vehicle standards).

With added support, HEI's future work in Asia, South Asia, and elsewhere will enable HEI to provide much-needed science on effects in local populations, which can also inform, through extrapolation, 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 University, Fudan University, IIT Bombay, U.S. National Aeronautics and Space Administration, University of British Columbia, and others) to employ cutting-edge satellite data, multiscale 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, as well as HEI's careful communication to decision makers, builds trust and fosters the reliance on high-quality, consistent science for local decisions.

Europe and Other Developed Areas

In Europe and elsewhere in the developed world, HEI's engagement reflects the established priorities laid out in the body of this Strategic Plan, which provides targeted research relevant to the needs of HEI's core sponsors, including government and industry, 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 the following:

- Studies of the effects of low levels of air pollution;
- Studies of the health impacts of exposure to traffic-related air pollution; and
- Studies of UFPs, NO_x, ozone, and advanced-technology internal combustion engines.

These and related research areas will help inform consideration of European limit values, emissions ceilings for vehicles, and national and city-level decisions about

traffic management 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 those in East Asia and South Asia, air pollution levels 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 socioeconomic 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 of pollution 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 added funding, focus on several key areas:

- *Global Burden of Disease*: HEI will continue to work with IHME, providing leadership on its Air Pollution Working Group. HEI will continue to annually update health and monitoring data, including the addition of information from new studies and satellite and ground-level monitoring; refine methods to estimate exposure–response functions; and evaluate and add new health endpoints and pollutants (e.g., birth outcomes, asthma, and NO₂ concentrations) for inclusion in GBD 2020 and beyond.
- *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 countries. These data are expected to aid health-based air quality management (e.g., key sources and fuel choices) in countries with limited ability to acquire this information on their own (e.g., many countries in 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, resulting in, for example, shifts in main power sources and 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 subsequent reports 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 with SoGA 2020 and continuing in future years, HEI will:
 - report on the addition of new health outcomes;
 - enhance the ability for visitors to our website to track concentrations of ozone and other pollutants; and
 - 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 is 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, which would be informative in refining estimates of health impacts in these same populations (e.g., in the integrated exposure–response [IER] curve used in the GBD). Under its new Plan, HEI aims to complete, peer review, and publish the Asian air pollution cohort studies being undertaken by Vermeulen and colleagues and to identify and report on key science gaps and opportunities that may exist in Asian cohorts. HEI will seek to support studies to fill those gaps, pursuing a capacity-building model designed both to enhance the skills of local scientists to conduct such research in the future and to produce results with maximum credibility to local officials.

CROSS-CUTTING ISSUES

In reviewing these detailed major opportunities that HEI plans to 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 in the earlier discussions of specific research areas. They are also pertinent for future research throughout this Strategic Plan period.

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 the replicability and reproducibility of the studies underpinning regulations (including issues such as data access, quality, and analyses). Additionally, reproducibility of studies in the broader scientific literature is the focus of recent debates in scientific journals and is also reflected in the U.S. government's attention to transparency.

Second, the strength and limitations of study methods, including the potential for introduction of bias, are subjects of legitimate 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 effects. 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. 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 the Strategic Plan 2020–2025 period, 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 earlier under "Major Accomplishments," the Institute will work with the investigators of the low-level exposure studies, as well as HEI's other studies, to make their data and codes available.

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 U.S. 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 (Special Report 17, 2010), a discussion of health effects of UFPs (Perspectives 3, 2013), diesel epidemiology studies among miners and truckers (Special Report 19, 2015), and health effects of exposure to new-technology diesel engines (Research Report 184, 2015).

The process for performing and synthesizing reviews has been evolving, and recently 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 currently reviewing the health effects from exposure to traffic-related air pollution has adapted procedures for its review work, and their protocol was published in summer 2019 on the HEI website (www.health-effects.org/system/files/TrafficReviewProtocol.pdf).

During the Strategic Plan 2020–2025 period, HEI will finish and disseminate this systematic traffic review. The Institute will also convene periodic workshops and meetings of experts in systematic review from multiple fields (e.g., at each HEI Annual Conference) to identify and help

implement enhanced principles learned through its work in order to advance the state of such reviews. It will, at the same time, explore whether there are enhanced ways to design bodies of studies — from their inception — to increase their ability to be later compared, contrasted, and considered in systematic 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 we find enhances the effectiveness of developing and testing 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:* This 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 spatiotemporal data that can be applied to the entire United States, which is a highly complex endeavor. HEI will be looking for opportunities to fund other approaches to causal modeling under its Accountability program. HEI has recently issued an open RFA (20-1, *Health Effects of Air Pollution*) to seek out new studies to advance these methods.
- *Other enhanced statistical techniques:* In its new Plan, HEI will continue its more than 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 multi-pollutant 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 oversee and review exposure assessment. Even as those individual studies proceed, HEI continues to look for ways to improve the techniques for exposure assessment for application in future studies.

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

- First, as discussed above, HEI's recent RFA (19-1) will fund five new studies to advance exposure assessment for air pollution and health studies using sensors, mobile monitoring, tracking technologies, and other approaches. The studies will 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 further 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 PM in air pollution from NASA's Multi-Angle Imager for Aerosols (MAIA) satellite.
- Third, as noted under "Transport and Urban Health" above, there are a number of components of the transport exposure mix that continue to attract attention for their potential shorter-term exposures and effects. HEI will continue to monitor these issues and identify roles that the Institute might play in improving assessment of these exposures.

Sensitive and At-Risk Populations

Laws to improve air quality in the United States, 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 the 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 disease, and other diseases whose underlying pathophysiology makes them more vulnerable; and those who are of lower socioeconomic status 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.

IMPLEMENTING THE STRATEGIC PLAN 2020–2025

Based on extensive comments from HEI’s Board of Directors, sponsors, other stakeholders, HEI Committees, and others in the scientific community — and the priority opportunities identified above — it is clear that, while we must of necessity plan for specific actions we will take in the next five years, HEI should do that with a clear eye on the much longer time frames for future air quality and climate decisions. Challenging questions surrounding air quality standards decisions continue to arise around the globe as the science evolves, and the technology to meet GHG goals (e.g., for vehicles and stationary sources) continues to change, raising issues beyond the time frame of this Plan. Given that, the HEI Strategic Plan is built around one overarching theme: *informing air quality and health decisions for 2020–2025...and beyond*.

The specific actions we plan to take are described below and in the attached timeline (Figure 7). Driven to inform the many upcoming policy decisions summarized across the top of Figure 7, HEI has identified five specific activities to be undertaken in five key areas of focus in implementing the Plan:

- Accountability: Testing the Links Between Air Quality Action and Health
- Complex Questions for the Air Pollution Mixture
- Transport and Urban Health
- Global Health
- Cross-Cutting Issues, including enhancing transparency throughout HEI’s work

While the HEI Strategic Plan is designed to be a clear path forward for us 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 also build in the flexibility to anticipate and act on the unanticipated, and we fully expect to continue to have that capacity in the coming years.

ACCOUNTABILITY: TESTING THE LINKS BETWEEN AIR QUALITY ACTION AND HEALTH

To effectively carry out the next generation of accountability research, and consistent with other areas of the Strategic Plan, HEI will strengthen its ability to track and take advantage of upcoming regulatory interventions in Europe and the United States:

- First, HEI will complete and communicate the results of two Accountability studies it has underway, examining the potential impacts of major interventions to improve air quality. These studies are focused on:
 - implementation of the California Goods Movement plan; and
 - transportation emission reductions in the United States and Canada.

- implementation of the California Goods Movement plan; and
- transportation emission reductions in the United States and Canada.

Special attention will be paid to communicating the lessons learned to inform future studies and decisions.

- Second, in 2020 HEI will launch new targeted studies aimed at key interventions and opportunities (e.g., those to reduce emissions from utilities and industrial sources; school bus retrofits; changes in household energy use; local traffic interventions; and efforts to reduce exposure for at-risk communities).
- Third, HEI will maintain an open RFA to seek out and support other new Accountability study opportunities as they arise.
- Fourth, HEI will conduct a multi-stakeholder workshop to examine what the lessons are from the challenges faced in the conduct of previous studies and how these lessons may be incorporated in the design of new studies, in particular at the low and high end of the concentration–response curve.

COMPLEX QUESTIONS FOR THE AIR POLLUTION MIXTURE

In this important area, HEI will, first and foremost, bring the major programs it has underway to timely completion and launch key studies already in the pipeline. These include studies on:

- the health effects of exposure to low pollution levels;
- at-risk populations and efforts to apply new methods to test causality;
- assessment of exposure to difficult-to-characterize pollutants such as NO_x, ozone, and UFPs; and
- continuation of regular testing and evaluation of statistical methods applied throughout HEI’s science programs.

At the same time, HEI will step back briefly at the start of the Strategic Plan to convene an expert panel to answer a basic question before launching new targeted research: *What future questions can science best answer?* At the start of the Strategic Plan implementation, this panel will advise HEI on the best approaches to several important questions:

- Should HEI further test the effects of low levels of exposure on health? This might potentially include initiating
 - follow-on epidemiological analyses from HEI’s initial large studies; and
 - potential mechanistic studies to test effects at low levels of exposure.

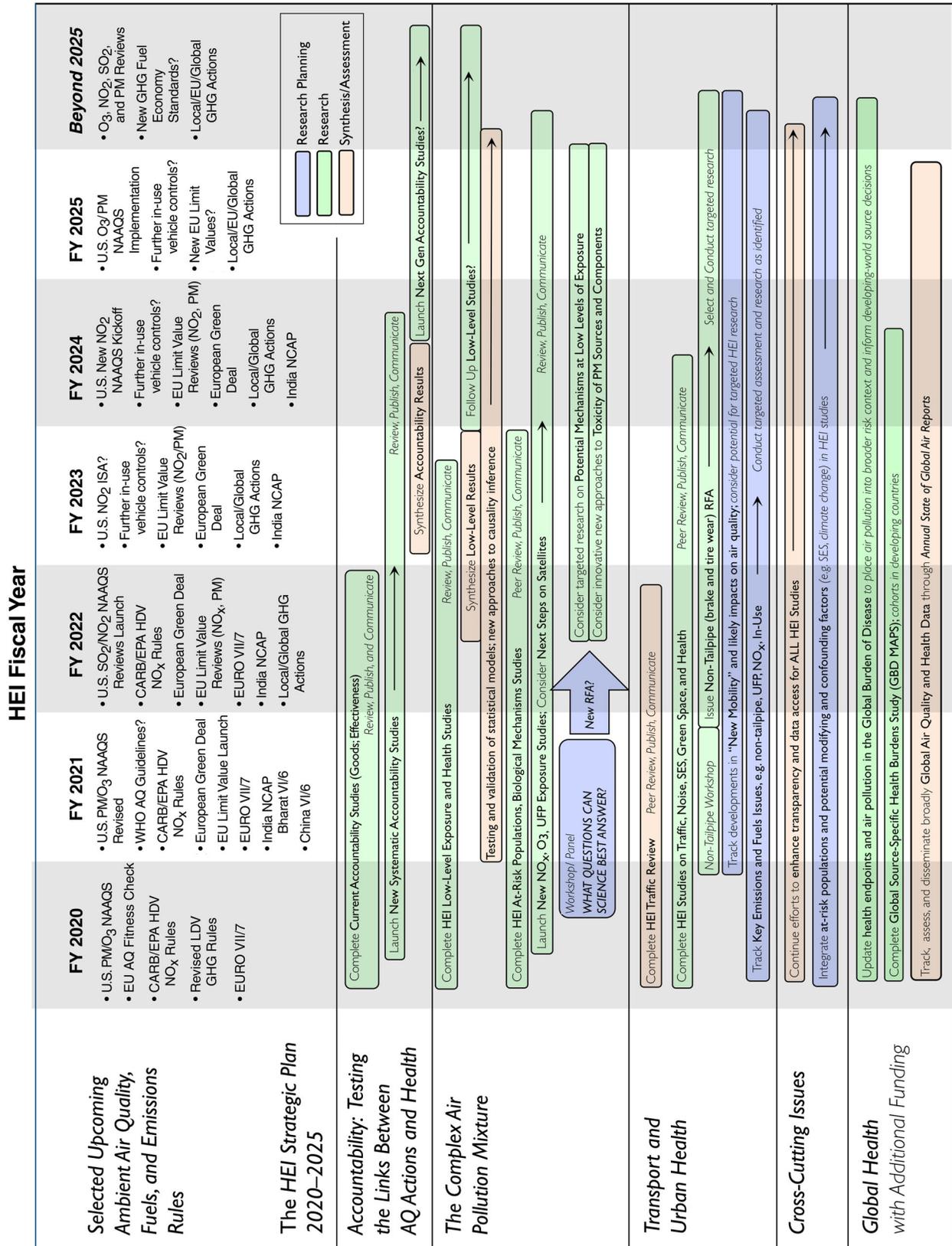


Figure 7. Implementing the HEI Strategic Plan 2020–2025.

- Can we build on HEI’s NPACT studies of the toxicity of PM components to identify whether there are new, more effective ways to further probe this important question?

Depending on the results from that expert panel, HEI will design and implement targeted programs of research to address one or more of these important topics.

TRANSPORT AND URBAN HEALTH

In order to provide time-sensitive information about the full range of potential effects of exposure to traffic, place that information in its broader urban context, and anticipate potential new mobility changes, HEI will:

- Complete and broadly communicate the work of the HEI Panel on the Health Effects of Long-Term Exposure to Traffic-Related Air Pollution — and identify new potential key priorities;
- Finish, peer review, and disseminate the results of HEI’s current studies placing transport in the broader context of noise, socioeconomic status, and green space; identify opportunities for follow-on investigation into broader urban health questions;
- Assess key emissions and fuels issues and conduct targeted assessment as needed;
- Evaluate and take action to better understand the potential exposures to and health effects from non-tailpipe emissions such as tire and brake wear; and
- Track and assess rapidly emerging trends in new vehicle technologies and use patterns (i.e., “new mobility”) and regularly evaluate whether there are important HEI-relevant questions arising.

GLOBAL HEALTH

HEI will continue to inform decisions taken in the developed world by seeking to:

- Target HEI research to projected U.S., EU, and other international policy trends and timelines, in the process strengthening bridges among HEI and international policy makers to enhance integration of HEI science into key science decision document;
- Participate in key science oversight and evaluation groups for highly relevant studies (e.g., WHO Air Quality Guidelines and the Global Burden of Disease updates); and
- In the developing countries of Asia and elsewhere, with added resources,

- Apply the GBD methods and data to estimating burdens from specific sources globally;
- Complete current and selectively undertaken new studies, as funding becomes available, including studies on the potential long-term effects of exposure to higher levels of pollution, in the process strengthening HEI’s ability to build science capacity; and
- Enhance HEI’s ability to communicate the results of its research to government, industry, development banks, and other stakeholders, building on and improving its annual State of Global Air initiative.

Taken together these activities will maintain HEI as a domestically and globally relevant provider of independent science that is regularly called on to credibly inform key decisions affecting public health and potential regulation in priority international forums.

CROSS-CUTTING ISSUES

In HEI’s planning, a number of specific health effects questions emerged that would not by themselves be programs of research in the new Strategic Plan, but which should be viewed as cross-cutting issues that could be integrated into all of HEI’s work. These include:

- Transparency in policy-relevant science, including
 - Data access and transparency;
 - Systematic synthesis of information on important issues; and
 - Testing causality through innovative statistical techniques, and other enhanced statistical techniques;
- Sensitive and at-risk populations; and
- Enhanced exposure assessment.

CONCLUSION

In sum, during the past five years HEI has continued to make substantial progress in providing timely, relevant, and credible science to inform air quality decisions. Building on that base, HEI stands poised to make even more targeted contributions in the years to come. We look forward to working with our scientific committees, our sponsors, and the broader community of stakeholders in air quality and health to continue to make lasting contributions of trusted science to inform better policy decisions for cleaner air and improved health.

ABBREVIATIONS AND OTHER TERMS

ABaCaS	Air Benefit and Cost and Attainment Assessment System	IHME	Institute for Health Metrics and Evaluation
ACEA	European Automobile Manufacturers Association	ISA	Integrated Science Assessment
ACES	Advanced Collaborative Emissions Study	LDV	light-duty vehicle
AQ	air quality	MAIA	Multi-Angle Imager for Aerosols
CONCAWE	Conservation of Clean Air and Water in Europe (research organization of the European oil industry)	MOSES	M ulticenter O zone S tudy in O ld E r S ubjects
CARB	California Air Resources Board	NAAQS	National Ambient Air Quality Standards (U.S.)
ESCAPE	European Study of Cohorts for Air Pollution Effect	NCAP	National Clean Air Program (India)
FHWA	Federal Highway Administration (U.S.)	NO ₂	nitrogen dioxide
GBD MAPS	Global Burden of Disease from Major Air Pollution Sources	NO _x	nitrogen oxides
GDI	gasoline direct injection	NPACT	National Particle Component Toxicity Initiative
GHG	greenhouse gas	RFA	Request for Applications
HDV	heavy-duty vehicle	PM	particulate matter
HEI	Health Effects Institute	PM _{2.5}	particulate matter ≤ 2.5 μm in aerodynamic diameter
IARC	International Agency for Research on Cancer	RDE	real driving emissions
IER	integrated exposure–response	SES	socioeconomic status
		SoGA	State of Global Air (program)
		UFPs	ultrafine particles
		VMT	vehicle miles traveled
		WHO	World Health Organization

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