Health Effects Institute

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

FIRST DRAFT

May 2019

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***** *We are especially interested in comments on these major opportunities!*

INTRODUCTION AND SUMMARY

We are pleased to provide you this First Draft of the HEI *Strategic Plan for Understanding the Health Effects of Air Pollution 2020 – 2025.* HEI's success at producing trusted science to inform key decisions relies on our ability to craft this 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 this 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 industrial stakeholders; and international, national, state and local agencies – to ensure that the HEI *Strategic Plan* targets our work at the most important topics.

We build this Plan upon the significant progress under the HEI *Strategic Plan 2015 – 2020* where, in just the first four years of implementing the plan, we have initiated, conducted, and/or completed over 50 studies, including major studies on health effects of exposure to very low levels of air pollution, new accountability and traffic related air pollution studies, to name just a few areas, and communicated our results in capitals throughout the US, Europe, and Asia. Each of our published reports – and their accompanying journal articles - have been cited in the scientific literature an average of 53 times by other scientists, and our work was cited extensively in key decision documents from US Environmental Protection Agency, the World Health Organization, the International Agency for Research on Cancer, and many more.

Looking ahead, we have already begun to identify key policy and science challenges for the coming years. We have been hearing as well from HEI sponsors and the scientific community of a number of major areas that HEI might address going forward – which at this point in Plan development includes more activities than HEI can expect to accomplish under this new Plan. ***Those major opportunities – on which we very much need your input – are described on pp. 26 to 37 and encompass four major areas of focus:***

- *Testing the Links Between Air Quality Action and Health* – building on HEI's accountability studies on key regulatory actions, exploring questions such as better methods for testing such links, whether such research help us test for causality and how they might help improve cost and benefit analyses for future actions. Studies soon to be initiated under a new Request for Applications (RFA) will address some of these questions but, given the complex nature of this issue, more research is clearly needed.
- *Complex Questions for the Air Pollution Mixture* – The difficult issues surrounding the complex air pollution mixture continue to challenge scientists and decision makers alike. HEI's Low Level Studies are testing concentration response relationships at the lowest levels and HEI's new RFA on exposure will seek and launch studies using sensors and many other new techniques to measure exposure to hard to characterize pollutants (NOx, UFP, etc.). To shed better light on the many questions that such research is raising, are there mechanistic studies needed to better understand complex exposures, and/or should HEI re-visit source-specific exposures and their differential effects? Should the health impacts of climate change, and actions to mitigate the impact of climate change, be a part of HEI's plans?
- *Transport and Urban Health* – A host of new innovations and other changes are making inroads and changing the future of transportation, even as the internal combustion engine will be in use for many years, and issues of in-use, non-tail-pipe, and other emissions continue

to arise. New questions are arising in this context, such as the health effects of ultrafine particles (UFP), as well as the role of factors such as noise, socioeconomic status, and access to green space. Anticipating the many diverse and potentially disruptive changes in transport, targeting the most significant continuing questions, and placing transport in the broader setting of urban health, will be key priorities for HEI going forward.

- *Global Health:* In the developing world, especially India and China, and elsewhere in Asia, rapid growth has raised levels of air pollution from all sources, and health science and policy decisions are just beginning to catch up to the challenge. With additional funding, HEI will continue and enhance its world-leading efforts to produce and communicate the results of Global Burden of Disease from outdoor air pollution, and produce improved science on the health effects of air pollution in developing countries, and a global analysis of the contributions to air pollution burdens from each source for every country in the world (GBD-MAPS Global).
- *A Key Cross-Cutting Issue:* Along with the opportunities mentioned above, we have identified a number of other issues that cross cut our programs. Most prominent among such issues is *Transparency in Policy-Relevant Science* – Data transparency and access 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. 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; this will be a hallmark of the HEI Strategic Plan 2020 - 2025. Other cross cutting issues – such as better statistical methods, susceptible populations, enhanced exposure assessment and capacity building – will continue to be an important part of HEI research and review activities.

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 as well build in the flexibility to *anticipate and act on the unanticipated*, and fully expect to continue to have that capacity in the coming years.

All told, these important areas cover a wide range of topics for which HEI's intensive research and special review capabilities could provide credible and policy-relevant answers. However, to help us sift through these possibilities systematically, and identify the most critical priorities for our *Strategic Plan 2020 - 2025* we need the input of the wide range of audiences we serve. We welcome your comments at a special session of our Annual Conference in Seattle, WA, on Tuesday, May 7, 2019 (see www.healtheffects.org/annual-conference for details). And please forward any further comments you may have to HEIplan@healtheffects.org .

PROGRESS: HEI STRATEGIC PLAN 2015–2020

PRIORITY RESEARCH AREAS

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 the last Strategic Plan 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 (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 development 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.

Emerging Technologies and Fuels

HEI has since its inception 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 new Plan proposed several areas of evaluation and potential research, including potential impact of the introduction of ethanol and gasoline direct injection, emissions of ultrafine particles and non-tail-pipe emissions (such as tire and brake wear).

Accountability and Transparency

HEI has provided a lead role in accountability research, further defining concepts and methods and initiating the next stage of new research in this challenging field examining the air quality and health impacts of actions to improve air quality. Having completed a substantial body of research, 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 studies funded under phase 2, which built on and extended beyond 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 and the more systematic linkage of accountability studies to the adoption of major new regulatory initiatives. HEI also extended its ongoing work on transparency and data access during this Plan.

Global Health Science

HEI built on key themes of accountability, multipollutant approaches and research at the air quality–climate nexus 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 upon to credibly inform decisions affecting public health and potential regulation in key forums in the developed and developing worlds. With added support from foundations, international sponsors, and in partnership with the European Union and others, HEI selectively enhanced its research program in the developing economies of Asia and Latin America, including support for global burden of disease from air pollution, source specific health impacts, life expectancy and other long term trends in worldwide air pollution and health.

ACCOMPLISHMENTS

MULTIPOLLUTANT SCIENCE

Estimating the Effects of Exposures to Low Levels of Air Pollution

Multipollutant Studies in Large Populations to Estimate the Effects of Exposure at Low Concentration

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 some epidemiologic studies reported adverse health effects even at levels lower than the U.S. National Ambient Air Quality Standards (NAAQS). Following an expert workshop in mid-2014 and an RFA issued later that year, HEI decided to fund three studies, engaging highly qualified multi-disciplinary investigator teams to examine air pollution and health relationships in very large cohorts in North America and Europe. The three studies are:

- **Michael Brauer**, University of British Columbia, Vancouver. *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.* 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.
- **Bert Brunekreef**, University of Utrecht, the Netherlands. *Mortality and morbidity effects of long-term exposure to low-level $PM_{2.5}$, black carbon, NO_2 and O_3: an analysis of European cohorts.* This study is conducting a pooled analysis in key populations from the European ESCAPE study, and companion analyses in six large administrative cohorts, with a total population size of approximately 25 million; and,
- **Francesca Dominici**, Harvard T.H. Chan School of Public Health, Boston. *Assessing adverse health effects of long-term exposure to low levels of ambient pollution, including development of methods for methods for causal modeling*. This study is conducting detailed and innovative analyses in the U.S. Medicare cohort, with a population size of over 65 million, with additional analyses in the Medicaid cohort and the Medicare Current Beneficiary enrollees cohort.

The strengths of the HEI program include:

- Application of HEI's well developed methods for study oversight, with a special oversight panel, and QA/QC 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 US, Canada and Europe, thus giving the studies an unprecedented statistical power.
- State of the art methods for exposure assessment, at high spatial resolution (1 km^2 or address level) using satellite data, chemical transport models, land use and weather variables and monitoring data, for fine particulate matter ($PM_{2.5}$), ozone, nitrogen dioxide (NO_2), and PM components, such as BC and non-tailpipe PM indicators in a subset.
- A wide range of mortality and morbidity health outcome, 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, multi-disciplinary investigator teams with extensive experience in cutting-edge research in exposure assessment, environmental epidemiology and statistical analysis.

The US and Canadian studies are 60 – 70% complete whereas the European study is nearly 80% complete. We anticipate final reports from the studies arriving at HEI during early part of the new plan; after review and commentary preparation, the research reports to be published in the early years of the new Strategic Plan.

While more detailed analyses are in progress, both the US 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 the two teams to submit Phase 1 reports, comprised of their analyses, results and conclusions from the first two years. HEI has formed a multi-disciplinary expert panel to review these Phase 1 reports and to prepare a commentary, discussing the research and the conclusions that may be drawn – which are expected to be further refined by continuing work. The investigators Phase 1 reports and the review panel's commentaries are expected to be published during summer, 2019.

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 **M**ulticenter **O**zone **S**tudy in Old**E**r **S**ubjects (**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:

- **John Balmes**, University of California San Francisco Medical School,
- **Phil 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., hours and days before experimental exposures at the laboratory). The report from the latest analyses is currently being reviewed by the MOSES review panel and the report, along with the panel's commentary, will be published in late 2019.

Examining Exposures and Health Effects from Traffic and Port Source Mixtures

Completion of Exposure Studies Previously Undertaken

Despite significant progress in the control of tail-pipe 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. Among other research needs, the review identified a paucity of reliable information on human traffic exposure as a major gap in knowledge.

Initiating a new research program on traffic-related air pollution, HEI funded five studies to improve exposure assessment to traffic-related air pollutants, and additional studies of non-tailpipe emissions (such as brake and tire wear) near roadways and a study of air pollution in tunnels. Three of these studies have been published (**Ben Barratt, Jeremy Sarnat, Xiaoliang Wang**), while two others -- **Stuart Batterman and Chris Frey** – are in the midst of the review process. Two studies on non-tail pipe emissions -- **Petros Koutrakis and Meredith Franklin** – are ongoing.

Launching a New Research Program

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, socio-economic 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 SES. HEI is now funding three additional studies (**Payam Dadvand and Jordi Sunyer; Meredith Franklin; Ole Raaschou-Nielsen**). Work on each of these studies is underway.

Diesel Emissions and Health Effects

Early during 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 in miners and truckers, each group exposed to emissions from old technology diesel engines. The second report was a comprehensive and succinct summary of an extensive HEI program – *the Advanced Collaborative Emissions Study (ACES)* – 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, a large number of 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 and charged with evaluation and synthesis of the associations of long-term exposure to traffic-related air pollution and the epidemiologic evidence for selected health outcomes, keeping in perspective the influence of other factors such as noise, SES and green space. The panel consists of the following members:

- Francesco Forastiere, Co-Chair (King's College London, UK)
- Frederick Lurmann, Co-Chair (Sonoma Technology, Inc., Petaluma, CA)
- Richard Atkinson (St George's, University of London, UK)
- Jeffrey Brook (University of Toronto, Canada; Member Research Committee)
- Howard Chang (Emory University, Atlanta)
- Gerard Hoek (Utrecht University, Netherlands)
- Barbara Hoffmann (University of Düsseldorf, Germany; Member Research Committee)
- Sharon Sagiv, University of California, Berkeley
- Audrey Smargiassi (University of Montreal, Canada)
- Adam Szpiro (University of Washington, Seattle)
- Danielle Vienneau (University of Basel, Switzerland)
- Gregory Wellenius (Brown University, Providence)
- Jennifer Weuve (Boston University, Boston)

The panel began its work in mid-2018, and has developed a protocol, risk-of-bias tool, and other instruments for its review; it has now begun literature searches and data extraction. Intensive work continues during 2019, with the report expected to be published, after peer-review, in late 2020.

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 has 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 specifically on exposure assessment of outdoor air pollutants whose levels vary greatly in space and time, such as nitrogen oxides, ozone, and ultrafine particles. Applications are expected in 2019, with studies to begin in early 2020.

ACCOUNTABILITY AND TRANSPARENCY

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

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 long-term actions to improve air quality at a regional and national level, assessing actions targeted at major ports, and improving statistical methods:

- Published reports on: Causal inference methods for estimating long-term health effects of national air quality regulations by **Corwin Zigler** (May 2016), the effects of policy-driven air quality improvements on children's respiratory health in Southern California by **Frank Gilliland** (January 2017), and impacts of regulations on air quality and emergency department visits in the Atlanta Metropolitan Area, 1999–2013 by **Armistead Russell** (April 2018).
- After completion of a pilot phase, a fourth study on improvements in air quality and health outcomes among California Medicaid enrollees due to goods movement actions in California by **Ying-Ying Meng** will be completed in Spring 2019 (publication expected in 2020).

In addition, HEI supported accountability-related research through other programmatic initiatives:

- A study to quantify 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 studies, HEI continues to engage in other activities that include leadership by publishing literature reviews (listed below) as well as organizing conference symposia, and participation in research planning activities:

- *Accountability Studies on Air Pollution and Health: the HEI Experience* in Current Environmental Health Reports, 2017 (4):514-522, by **Boogaard, van Erp, Walker, and Shaikh**
- *Assessing health effects of air quality actions: what's next?* In Lancet Public Health, Vol 4 January 2019, by **Boogaard** and **van Erp**
- Cochrane Review: *Interventions to reduce ambient particulate matter air pollution and their effect on health (Protocol)* by Burns, **Boogaard**, Turley, Pfadenhauer, **van Erp**, Rohwer, and Rehfuess. 2019. DOI: 10.1002/14651858.CD010919.pub2. This work also presented in several poster sessions at various conferences, including WHO workshops on Air Quality Guidelines

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, A*ssessing Improved Air Quality and Health from National, Regional, and Local Air Quality Actions*, in December 2018 to solicit a third wave of accountability studies. Twenty-eight preliminary applications were received in February 2019. Ten applicants were invited to submit a full application for a funding decision in the Summer of 2019.

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 public access to data generated during HEI studies include (for full details and list of older studies, visit *www.healtheffects.org/research/databases*:

- **Francesca Dominici** and her colleagues, who are conducting the US study on effects of low levels of air pollution, are have efforts underway to provide access to their data and analytical methods (health data used in these studies, obtained from Medicare and Medicaid Services, cannot be made public in compliance with federal regulations).
- Data from the ***Multicenter Ozone Study in Older Subjects*** **(MOSES)** at the Harvard Dataverse (https://dataverse.harvard.edu/)
- Data sets from the **Wang** study, containing information on real-world emissions in two traffic tunnels in Hong-Kong and Baltimore, at the Harvard Dataverse (https://dataverse.harvard.edu/),
- Data from emissions characterization under the **HEI Advanced Collaborative Emissions Study (ACES)** can be obtained from the website of HEI's partner, the Coordinating Research Council, for Phase 1 https://www.crcao.org/reports/recentstudies2009/ACES%20Phase%201/ACES_Final_Database_JUNE2010.zip and for Phase 2 https://www.crcao.org/reports/recentstudies2013/ACES%20Ph2/Database%202013.12.16.zip.
- HEI also maintains a number of other data bases that are available through our website (*www.healtheffects.org/research/databases)*

EMERGING FUELS AND TECHNOLOGIES

HEI has long provided critical information on key emerging questions relevant to 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.

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 to meeting the latest US and California standards. HEI published an Executive Summary of this workshop which highlighted the salient findings of presentations and discussions during the workshop.

Ultrafine particle (UFP) emissions and their potential impact continue to be an area of interest and measurements and effects of ultrafine 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 above, HEI has 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-Tail Pipe Emissions As the use of diesel particulate filters, and other technologies, decreases the overall emissions of PM from the tailpipe, non-combustion emissions of PM are receiving more attention, 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.

- **Petros Koutrakis** (Harvard Chan School of Public Health), Chemical and physical characterization of non-tailpipe and tailpipe emissions near major roads in the Boston Area,

and

- **Meredith Franklin** (University of Southern California), Intersections as hot spots: Assessing the contribution of localized non-tailpipe emissions and noise on the association between traffic and children's health.

GLOBAL HEALTH SCIENCE

In the context of sustained interest and demand for HEI science in its core domestic arena, HEI has worked systemically and carefully to extend the scope of its science to be globally relevant by obtaining supplemental support from a range of philanthropic, governmental, industrial and banking sources. This funding leverages core funding to enable HEI to support a broad portfolio of 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 (Global Air Quality Guidelines for major pollutants), and the European Commission (European Limit Values for $PM_{2.5}$, NO_2, CO and some air toxics) and effectiveness of air quality actions and regulations, and these same studies are designed to also inform decisions in the United States.

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

Taking a global perspective uniquely positions HEI to inform understanding of health effects along the entire exposure response spectrum, have a policy impact in highly polluted highly populated areas, and provide science to inform regulatory decisions at the source, providing air quality benefits to local populations, reducing transport to Japan and North America, and providing a health based rationale for moderating greenhouse gas production in developed and developing countries.

Supporting broadly relevant studies in Europe

As reported in detail earlier, from 2015-2020, HEI has initiated or completed a range of studies in that directly inform decisions in the United States in priority research areas of multi pollutant science, emerging technologies and fuels, and accountability, even as they contribute to local knowledge. Representative examples in the global arena include:

- A study of low-level effects of ambient air pollution and mortality in large cohorts by **Bert Brunekreef** and colleagues in Europe, with results expected for HEI review and publication in the first years of the new Strategic Plan;
- A study of exposure and health effects from traffic by **Xiaoliang Wang** evaluating how mobile-source emissions have changed by examining real-world emissions characterization in the Shing Mun Tunnel in Hong Kong and the Fort McHenry Tunnel in Baltimore, Maryland;
- A study that developed a dynamic three-dimensional land-use regression model for Hong Kong and used it to estimate exposure to traffic-related air pollution at ground level and upper elevations in urban areas by **Benjamin Barratt**.

Results of these and companion studies have been and will continue to be actively communicated in key European and globally relevant forums and scientific workshops, including at WHO, DG Environment, IARC, and to national governments as they consider evaluation of European limit values, national emission ceilings, and standards for stationary, mobile sources and other sources which, in turn, provide guidance to many developing countries as well.

Developing countries

In the developing world especially India, China, and elsewhere in Asia, rapid growth has raised the level of air pollution from all sources, yet health science is often lagging, limiting the ability to address this problem. HEI leveraged significant additional funding from foundation and other sources to provide key science, capacity building and communication in developing countries where levels of air pollution consistently exceed health based international and national standards.

HEI engagement is based on its experience that local health impacts, credibly presented and understood in a global context provides multiple benefits, including credible science to inform decisions in the emerging vehicle and technology markets, high quality health-impact information and source specific health effects to guide informed air quality management and mitigation of emissions in Asia, reducing air pollution transported to Japan and the Western US. At the same time HEI has built capacity and fostered international cooperation by working with leading scientists and institutions in key parts of the developing world side by side with leading western investigators.

Key results from HEI's global program include:

Support for the Global Burden of Disease (GBD), the most comprehensive and credible worldwide assessment of all major risk factors associated with death and disease. Now produced annually, GBD is produced by the Institute for Health Metrics and Evaluation. HEI and our partners provided leadership the air pollution analysis for all GBD releases from 2015-2020 and worked with IHME and others to communicate country 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 5th highest ranking risk factor for mortality worldwide, behind measures of only diet, blood pressure, tobacco and blood sugar. For the first time, air pollution impacts were calculated including the addition of diabetes as a key health outcome and will be further expanded in coming editions.

Source Specific Impacts of Air Pollution The developing world faces significant limitations on air monitoring and health data and, as a result, information on source specific health impacts. Such information is key to educating the public about key sources and enabling regulators and stakeholders to make informed choices about health-based air quality management, now and projecting into the future to evaluate business as usual relative to alternative 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 US to publish:

- *GBD MAPS – China*, which identified emissions from the industrial, energy and domestic coal as a concern now and looking forward, and
- *GBD-MAPS – India*, which found residential biomass anthropogenic dusts and coal as sources with major health impacts.

State of Global Air During the last 5-year strategic plan, with supplemental 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 to report on the levels and

burden of air pollution for every country in the world, in some cases providing data at the provincial level (e.g. China) in a current, searchable database. SoGA provides data on levels of air quality in each country mortality impacts from major diseases impacted by air pollution, and air pollution and mortality trends from 1990 through 2017, providing 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 only GBD, including results from WHO, IEA, World Bank and other analysts, enhancing understanding of differences and similarities in methods and results worldwide in a single location.

- SoGA 2017: Introduced data on the significant global mortality impact of air pollution and worldwide and those regions that are most and least affected
- SoGA 2018: Updated the above information and focused in depth on tacking trends in India and China, and the significant burden of household air pollution
- SoGA 2019: Provided new information on life expectancy, the addition of diabetes as a risk factor and signaled progress in China with initial declines in air pollution.

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 While many results of studies in other parts of the world can be applied in estimating health burden of air pollution, the acceptance of those estimates can be enhanced by attempting to produce selected additional studies for key questions, e.g. estimating health burdens at high ambient levels. To that end, HEI in 2017 funded a team led by **Roel Vermeulen**, et al that is applying air pollution exposure estimates to pre-existing and well characterized population cohorts in a number of Asian cities.

CROSS-CUTTING ISSUES

Many studies mentioned in the previous sections address 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:

- Studies to *advance statistical methods* to more accurately understand and interpret data from epidemiological studies (Molitor, Park, Zigler, Coull, Batterman). Additionally, under the HEI program on 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 *susceptible populations.* HEI supported studies in this area include research in the young (Gilliland), pregnant women (Lee, Qian, Wu) and the elderly (MOSES), and in individuals with asthma (Pedersen).
- *Enhanced exposure assessment*, as discussed above, is a key component of many HEI studies (for example, the exposure to low-levels of air pollution and traffic studies) and HEI investigators are developing and applying advanced techniques, using data from satellite data, chemical transport models, land use and weather variables and monitoring data, for state-of-the-art exposure assessment at wide geographical scales. In addition, HEI has funded other research to improve exposure assessment and has just issued an RFA focused specifically on exposure assessment of outdoor

air pollutants whose levels vary greatly in space and time, such as nitrogen oxides, and ultrafine particles.

- Studies examining *other health outcomes and modifying factors,* including reproductive effects and pregnancy outcome (Dadvand, Wu, Qian, Molitor); neurocognitive outcomes (Chen) and autism (Guxens), as well as noise (Franklin, Raaschou-Nielsen) and socio-economic factors (Clougherty, Raaschou-Nielsen).
- Studies focused on *mechanisms* that are important in forming and transforming air pollutants in the atmosphere (Surratt; Ng), or in producing toxicologic effects (Contreras, Fryer, Gowdy, Shiraiwa).
- *Capacity building*, by supporting early-career investigators to focus their research on environmental health issues; since 2015, HEI has funded five such investigators under its prestigious Rosenblith Award, including Gowdy, Guxens, Apte, 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 decisions and advancing understanding across the scientific community. HEI is also strongly committed to tracking the Institute's progress in meeting these goals is. HEI initiated and completed a large number of projects that were 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 is summarized below.

Studies Started and Completed

HEI initiated 21 studies of air pollution health and exposure over the first four years of the 2015-2020 Strategic Plan and published 30 reports. This number includes several reports that were large, complex, and multipart (such as the MOSES report). HEI published five communications and special reports, including publications focused on Diesel Epidemiology and China and India source-specific burdens. At the start of the last year of the Plan, HEI has six reports in its review and publication process (including MOSES Part II and Phase 1 reports from the Dominici and Brauer low level exposure studies). HEI also maintains data from key studies at publicly accessible websites and, from time to time, other air pollution data.

Study Dissemination

Since its inception, HEI has distributed scientific reports and summaries of those reports (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 through *www.healtheffects.org/publications*. Our website 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 via the Web. 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 and Special Reports, HEI Statements, and other documents. In addition, HEI's new State of Global website 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. So far, 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 its scientific reports. HEI recently analyzed the extent to which HEI Research Reports and scientific papers resulting from HEI supported work, published in 2015 through April 2019, have been cited in the scientific literature. Results of this analysis suggest that HEI's impact is substantial (Figure 1).

- The 30 HEI reports published through Year Four of the Plan were cited 169 times in more than 50 health and atmospheric science journals (since some of those reports were only published recently, we would expect citations to rise in the coming years).
- The work described in the 30 reports also resulted in 59 peer-reviewed scientific articles; these

peer-reviewed publications, in turn, were cited 1426 times in other publications.

- Thus, the 30 HEI-funded research reports during 2010-2014 generated an average of 53 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 23 studies that are currently in progress and their peer-reviewed publications, nor does it include HEI reports and publications prior to 2010 which continue to be cited.

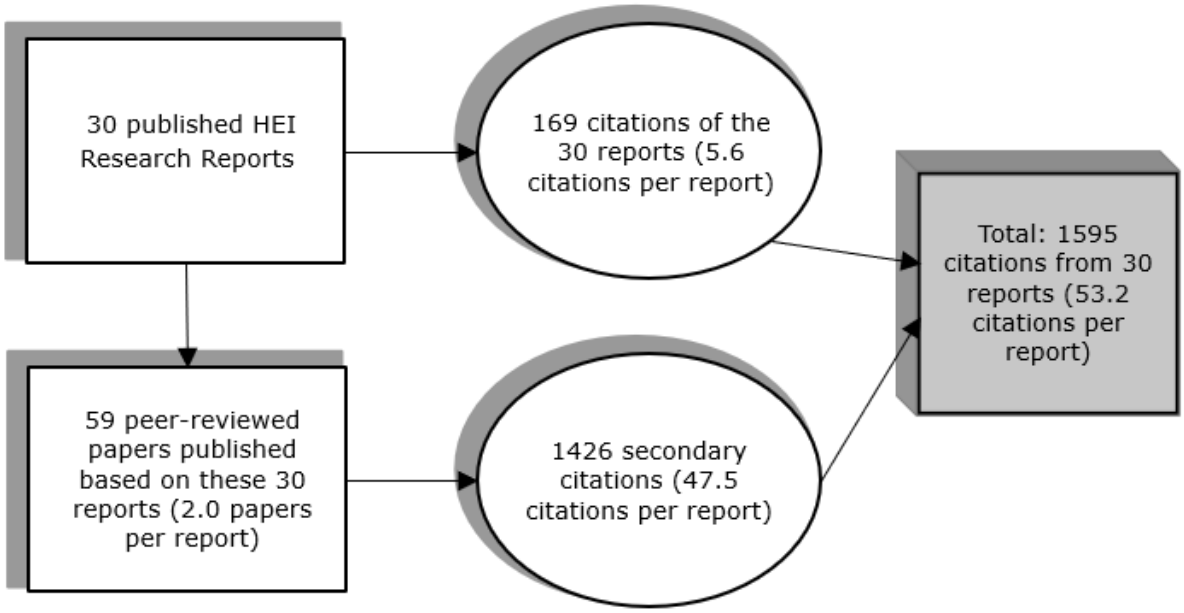


Figure 1: Citations of HEI reports (published during 2015 - 2019) and accompanying journal articles in the scientific literature. *(Numbers in parenthesis are average per report).*

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 US and elsewhere. For instance, Figure 2 illustrates a continuing role in the EPA's last four reviews of the particulate matter ambient air quality standards. And this impact is likely significantly understated, as it only includes actual HEI reports cited in the ISA; as noted above, for each HEI report there are at least two journal papers produced as well whose citation in the ISA is 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 as well.

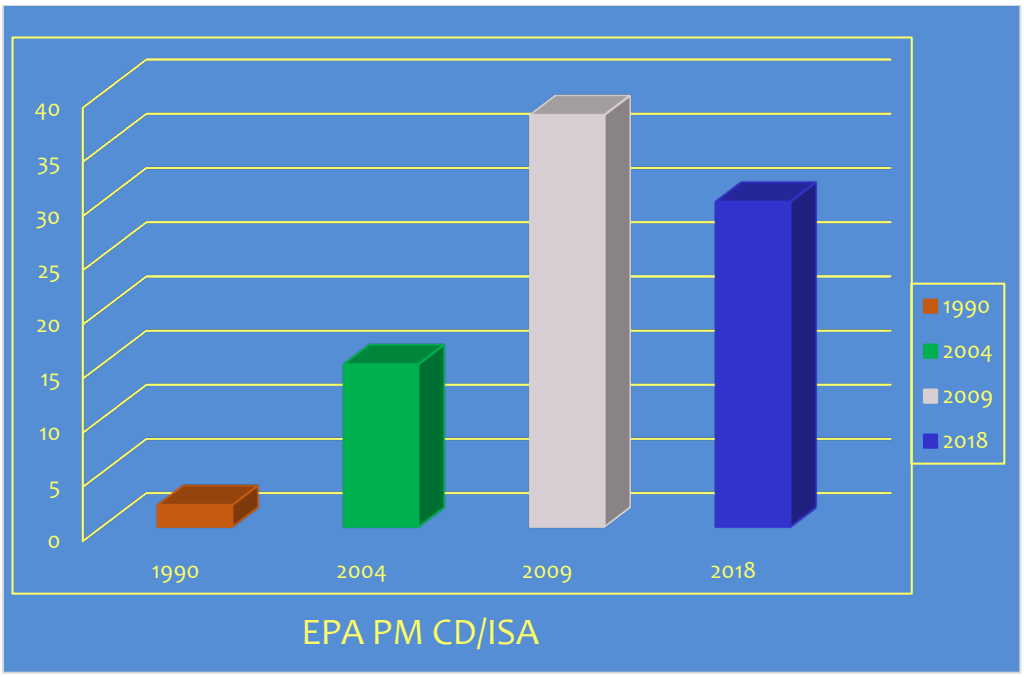


Figure 2. Citations of HEI reports in Key US EPA Scientific Summaries

(Note: the 2018 EPA document is a draft and not the final ISA).

Communication does not end, of course, with the citation of an HEI report in a regulatory document. HEI engages in *frequent outreach to leadership and staff from EPA and core 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:

- *US Governmental agencies and legislative bodies:* The U.S. Congress; Federal Highway Administration, National Institutes of Health, Occupational Safety and Health Administration, Department of Energy, California Air Resources Board;
- *Public and private advisory bodies:* The National Academies of Science, Engineering and Medicine; Clean Air Act Advisory Committee; 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 (ABaCaS) Meetings); India Ministry of Environment, Forests and Climate Change;
- *Private sector associations and public interest groups:* American Forest and Paper Association; American Lung Association; American Petroleum Institute, CONCAWE; Auto Alliance; ACEA; Engine Manufacturers Association; Environmental Defense Fund; European, US, and Indian Emission Control Manufacturers; Natural Resources Defense Council; Union of Concerned Scientists.

THE CHALLENGES AHEAD: The Policy and Science Context

POLICY CHALLENGES

Identifying the highest priority needs and concerns of air pollution policymakers 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 U.S. 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 which stress issues such as: potential unaddressed human health impacts, even at very low pollutant concentrations; characterizing 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 sources and more powerful means of assembling, managing and sharing of 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

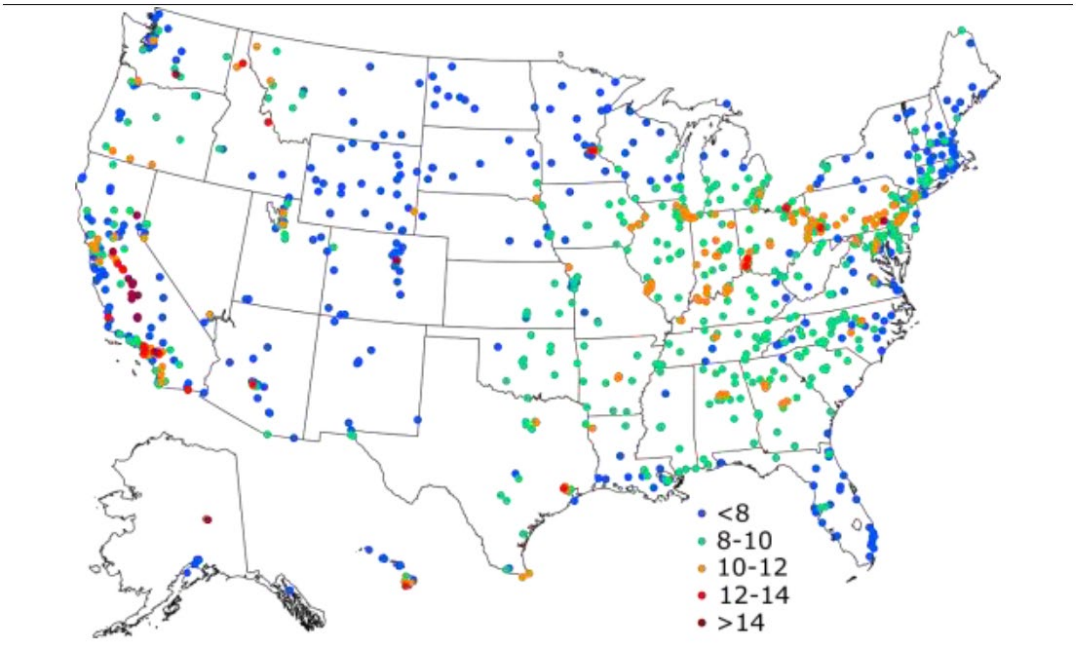
The review of the latest science on particulate matter ($PM_{2.5}$), ozone, nitrogen dioxide (NO_2) and other pollutants – and the consideration of current and future ambient air quality standards - is continuing at a sustained pace in the US, Europe, and globally. Specifically:

- In the ***United States***, the U.S. Environmental Protection Agency has recently completed the review of the U.S. National Ambient Air Quality Standards (NAAQS) for NO_2 and is deep into the review of the science for the NAAQS for $PM_{2.5}$ and ozone. These latter have a nominal target for completion by the end of 2020, with implementation to follow throughout the 2020s.
- At the ***World Health Organization,*** the review of the Worldwide Air Quality Guidelines is proceeding forward with the planned completion and journal publication of systematic literature reviews for the major pollutants, i.e. $PM_{2.5}$, ozone, NO_2, CO, and some air toxics, to be published in 2019 – and the completed reviews and establishment of guidelines likely to take place in the 2021 time frame. While these guidelines do not directly affect US standard-setting, they do play a significant role in the setting of European Limit Values as well as standards set in many countries around the world (e.g. China has set their $PM_{2.5}$ standard at a level (35 $\mu g/m^3$) equivalent to the highest tier of the WHO Air Quality Guidelines) and are of great interest to US and global industry.
- The ***European Union*** is currently conducting a *Fitness Check* review of its entire Limit Values setting and implementation program. That process – with extensive stakeholder input – is expected to be completed later in 2019. Following that — and pending the establishment of a new European Commission and election of a new European Parliament — the European Commission is expected to consider re-visiting the current Limit Values for $PM_{2.5}$, NO_2, and others.

- 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 have 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 problem has led to accelerated implementation of new standards for vehicles by 2020, expanded use of LPG for household fuel, and the launch of the first-ever National Clean Air Programme (NCAP). Significant implementation efforts are now being discussed.
    - In both countries and around the developing world there is a need for high-quality local science – especially on longer term effects - to inform the needed, 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 longstanding questions while others have arisen with more recent concerns.

- With levels of PM declining across the US (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 associations at very low levels of ambient concentrations are published.



Source Permission pending: U.S. EPA 2016 analysis of Air Quality System network data 2013−2015.

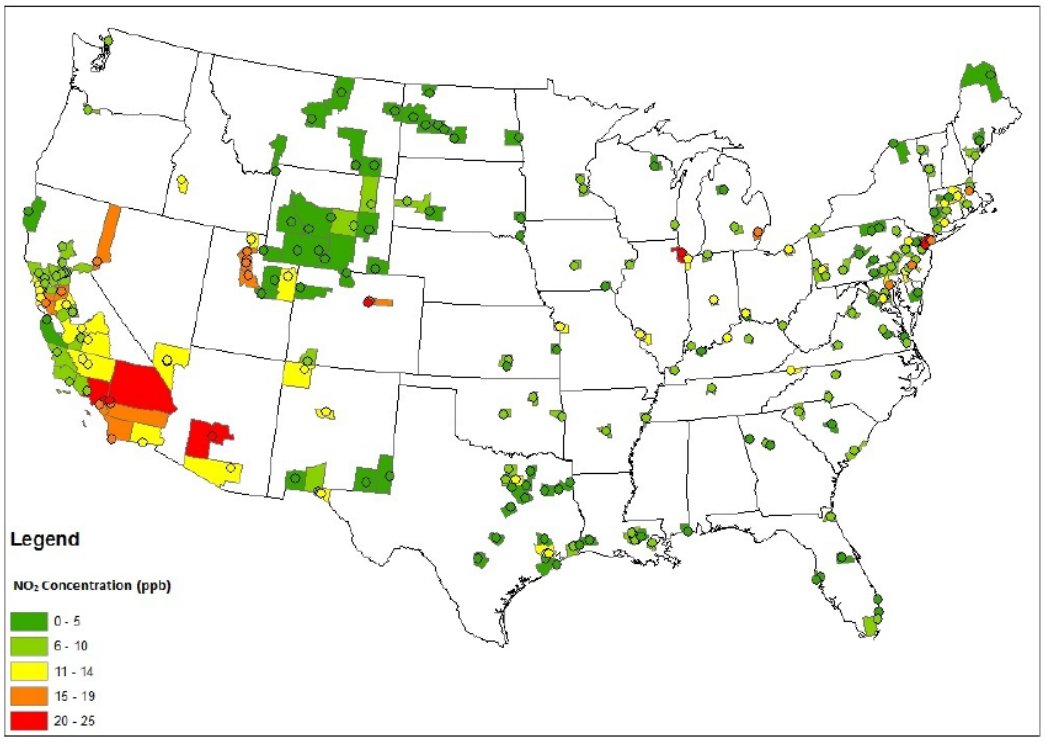
Three-year average $PM_{2.5}$ concentrations 2013−2015.

Figure 3 U.S.EPA Draft PM ISA OCTOBER 2018

- At the same time, the advent of these questions and publications about low-level associations has also 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 – which 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 NO_2 with somewhat different patterns of regulatory and policy activity on both sides of the Atlantic.
  - In the US, following an earlier review of the NAAQS for NO_2, a new network of roadside monitors was installed to monitor both NO_2 and $PM_{2.5}$. However, the relatively low levels of NO_2 found has led to a scaling back of those monitors for NO_2 and a decision to retain the current NAAQS, even while retaining the roadside monitors for $PM_{2.5}$. (see Figure 4)



Note: NO_2 = nitrogen dioxide. Concentrations indicated are the highest concentration in the county and do not represent countywide concentrations.

Source: U.S. Environmental Protection Agency 2014 analysis of data from state and local air monitoring stations.

U.S. annual average nitrogen dioxide concentrations for 2013.

Figure 4 U.S. EPA NO_2 ISA Final 2016

  - In contrast, in Europe, the higher levels of NO_2 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 US NAAQS – have resulted in many more locations facing a challenge of reducing NO_2 levels and exposure. (see Figure 5)

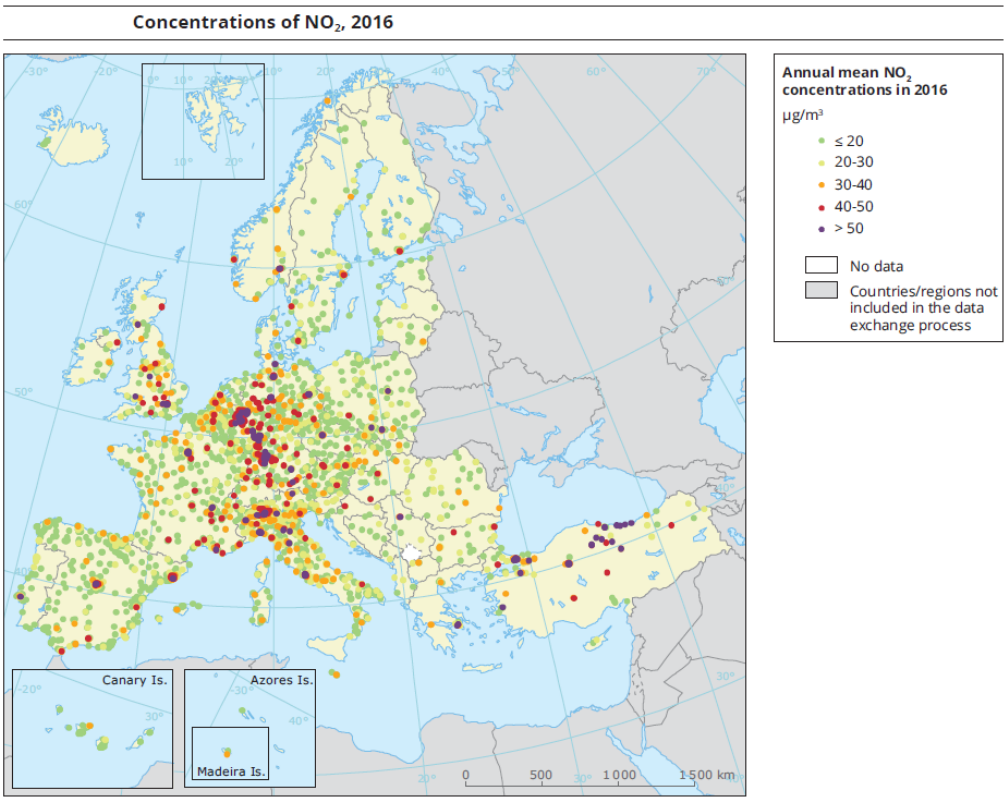


Figure 5 European Environment Agency Air Quality in Europe 2018

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 as vehicle ownership and miles traveled (VMT) grow, and despite significant achievements in reducing in vehicle emissions. At the same time new, potentially disruptive mobility technologies – 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 engines.

The continued growth 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/6 standards in India, China VI/6, potential new additional NOx controls in California and the US for heavy duty vehicles, and the initial discussions about a new EURO VII/7 in the coming decade. This newer wave of regulation is attempting to address a range of issues:

- Continued air quality concerns, particularly around ozone and the role of vehicle NOx emissions in the persistence of continued high ozone levels in some regions. This has been the case in California, where the challenges of ozone attainment are seen as demanding significant new actions, in part to address concerns that diesel emission control technologies may not yield the

expected NOx reductions from the 2010 rules; action which US EPA has expressed interest in beginning as well for other regions.

- Highly visible cases in both Europe and the US of problems with actual in-use emissions far exceeding standards are leading to far-reaching effort to control real driving emissions (RDE) in Europe and to strengthen in-use enforcement in the US.
- Rapid transitions in engine technologies and fuels, pursued for fuel efficiency or other goals, 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 ultrafine particle emissions. 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.
- Continuing and growing focus on reducing emissions from existing fleets, including funding of retrofit and replacement of 'high-emitters,' and the new US roadside monitors (see Figure 6) which are likely to focus increased attention on PM exposures, even as NO_2 exposures have been found to be lower than expected.
- With the availability of low-cost sensors, the availability of widespread information on air concentrations – though of uncertain quality – is like to result in increasing pressure to control such community and neighborhood emission.

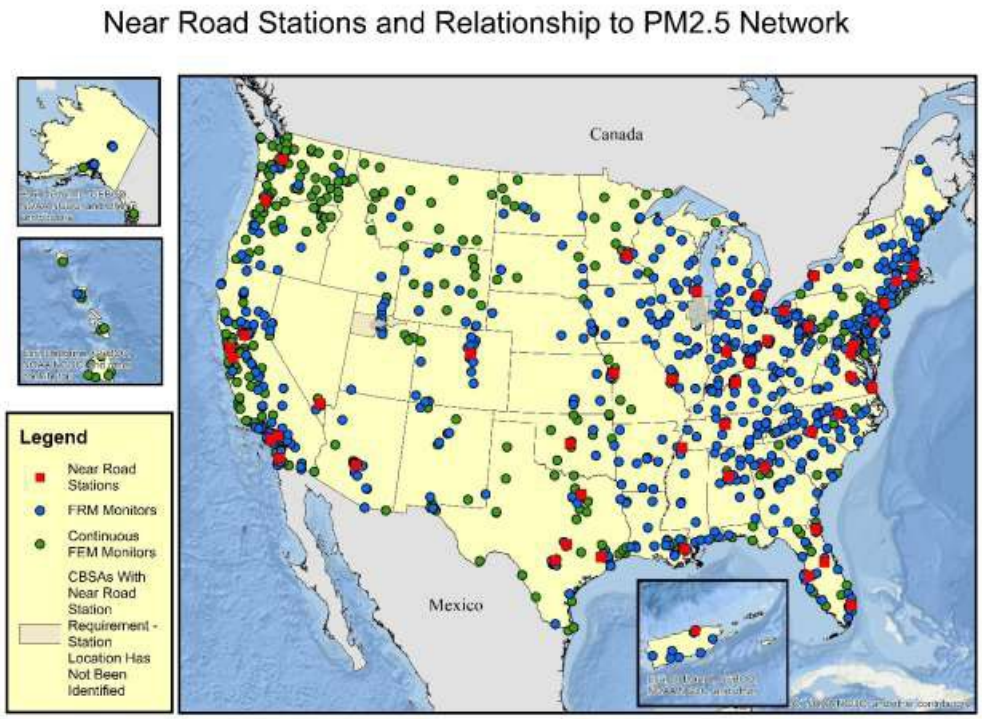


Figure 6. U.S. EPA Draft PM ISA October 2018

An 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, transparency of rulemaking, and the

ownership and control of the data underpinning scientific research in ways that are particularly relevant for air pollution decision-making.

- A key goal 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 health care – which 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 while meeting other imperatives heightens the value of sound models of reanalyzing and evaluating data.
- These issues also apply increasingly to enhancing the transparency and quality of any *systematic review* of scientific literature, including establishing a priori protocols, 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 an administration policy objective 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 to assessing exposures and health effects of air pollutants continues to pose significant challenges. The following are the highlights of some such challenges; in the "Major Research Opportunities" below, we discuss how HEI plans to approach them.

- *Effects of exposure to low levels of pollutants*: as we discuss above, evidence is emerging that even at and below the ambient NAAQS standards for PM and ozone, adverse health effects are 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 quality exposure assessments are needed for such studies, and methods for ensuring the highest possible control for confounders in these large populations remain challenging.
    - Further, the advent of large population results poses *a challenge to animal toxicology and human clinical studies* where small numbers of subjects and high costs makes testing of low-level effects difficult.
- *Information on large populations*: Perhaps the best source of health data on large populations is from census and health care utilization organizations (health insurance companies or federal programs). However, access to and analyses of such data are complicated by confidentiality and privacy issues, many of which are ensured under federal and state policies.
- *Newly developing methods for testing and determining causality.* HEI and other science has been investing in developing and applying new statistical techniques – causal inference statistical

models – to attempt to enhance the determination of whether a particular exposure *causes* an effect. These models are still in early 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 has well recognized limitations. Although there have been improvements in exposure modeling (e.g. land use regression) there now several emerging trends to attempt to improve exposure assessment. These include:
    - *Microscale exposure assessment*, in some cases taking advantage of new *low-cost sensors* to greatly expand intensive exposure measurement. These techniques can enhance coverage of and variability among 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 of the data, but also with increased challenges of risk understanding and communication.
    - Increased reliance on *satellite imaging data* for estimating PM concentrations – and increasingly for other pollutants -- in order to maximize the populations and areas available for analysis, but this approach has not been fully 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 using innovative new methods – including some employing uncommon approaches such as "citizen science" and exploitation of larger data bases 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 can be seen as valid.
- *Methods for assessing the toxicity of ambient air pollutants*: Although numerous methods to assess processes, such as genotoxicity, oxidative stress, mitochondrial damage, etc., 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 these methods further, to standardize their protocols, and to assess their ability to predict effects in humans.

THE 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 Complex Air Pollution Mixture
- Transportation 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 environmental regulations, providing a critical feedback loop to decision makers.

HEI's interest and commitment to accountability studies stems in large measure from the importance of assessing whether complex regulations and other interventions are actually yielding the improvements in air pollution and public health that were initially projected. Given that air quality has improved over the past decades, further improvements become more difficult to achieve and more costly. Early on, HEI defined initial concepts and methods with the publication of a major Monograph. Since then, HEI has funded two successful waves of studies that evaluated both local interventions occurring over relatively short periods of time as well as more complex, longer-term interventions at the regional or national level. Lessons learned about regulatory efficacy 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 late 2019. RFA 18-1 solicited studies in the following areas: (1) Long-term complex regulatory programs: studies that evaluate regulatory and other actions at the national or regional level implemented over multiple years; (2) Interventions at the local level: studies that evaluate actions targeted at improving air quality in urban areas, with well-documented air quality problems and programs to address them, including but not limited to low emission zones, congestion charging, and so-called diesel bans; (3) Ports and global transport: studies that evaluate regulatory and other actions to improve air quality around major ports (both marine and air) and transportation hubs and corridors; and (4) Methods development and dissemination: studies that develop, apply and disseminate statistical and other methodology for conducting such research.

Looking ahead to the 2020-2025 Strategic Plan, HEI plans to continue its leadership role in this area:

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, a new program of research – with studies funded under RFA 18-1 (see above) to be launched in late 2019 – will set the stage for the next generation of accountability research during the core years of HEI's new *Strategic Plan 2020 - 2025*. Such studies are a key underpinning of smart policy and regulation. They provide one of the few avenues for rigorously testing the links between emissions, exposure, and health. In addition to evaluating effectiveness of air quality regulatory actions, this program also aims to develop more robust research designs and statistical methods for estimating the health effects of air quality interventions.

New Methods:

HEI continues to foster development of new statistical methods to enable direct evaluation of well-defined, long-term regulatory interventions, for example by using national databases such as Medicare or census data or large cohorts. Because the effect on health of further reductions in air pollution are likely to be small, particularly in high income countries with low ambient levels, it is important to develop a sophisticated perspective on whether future studies will have the power to detect and quantify an effect — if there is one — and to describe a null effect with enough precision to be informative for policy purposes. It will be critical to pay serious attention to the sensitivity of statistical inference to model specification and time-varying confounding or implement quantitative bias analyses. Where possible, HEI is asking researchers to evaluate whether their study can add to the evidence base for a causal relationship between air pollution and health.

Specific Study Areas:

- National- or regional-scale air quality actions over the long term. In the US there have been 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.
- Air quality actions at the local (urban) scale. Recently, many cities have started to implement actions to improve air quality, e.g. congestion charging and low emission zones, limiting driving days for cars with certain license plate numbers, implementing road closures or restricted access of certain streets (e.g. Oxford Street in London), or outright bans of certain vehicles, for example diesel vehicles, mainly in Europe. These actions go hand in hand with efforts to transform urban mobility. Those new developments lead to growing attention on the fuller range of potential effects of transportation and mobility decisions on public health, including the positive effects of an increase in physical activity.
- Regulatory actions targeted at major ports and transportation corridors. Over the past decade, several states have started to develop complex programs to reduce emissions from "goods movement," by targeting marine vessels, harbor craft, railway locomotives, heavy-duty trucks, and cargo handling equipment that contribute to concentrations of particulate matter and nitrogen oxides, mostly from diesel engines. In addition, ports are often situated adjacent to densely populated areas, with a relatively high percentage of disadvantaged populations. Internationally, efforts have been made to reduce emissions from ocean freight in Emission Control Areas designated by the International Maritime Organization (IMO) to reduce air pollution emissions from ships that affect ports and coastal communities. Similar issues apply to airports, where there is a need for information on ultrafine particles and noise and effectiveness of measures to reduce their impact.
- *Environmental Justice:* Where possible, HEI asks researchers to focus on sensitive populations (e.g. children) who may be disproportionally affected, and on communities that may be at greater risk due to ethnicity, socioeconomic status, proximity to roadways and stationary sources, and the cumulative effects of multiple pollutants.
- And other relevant areas identified by investigators and stakeholders.

Complex Questions for the Air Pollution Mixture

Levels of ambient air pollution have generally declined over several decades in North America, Western Europe, and other high-income regions, due in large part to air quality regulation and technological improvements. The levels of many ambient pollutants today are 60 percent or more

lower than the levels 25-30 years, 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:

- An association 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 scales and health databases containing tens of millions of records, as well as developing new methods for meticulous statistical analyses, these findings raise questions about the level of protection offered by the current standards, at least for $PM_{2.5}$, and probably for ozone and NO_2 as well.

- HEI's NPACT studies – a systematic, multidisciplinary program that used coordinated toxicology, epidemiology and exposure assessment research to examine and compare the toxicity of PM components, and found that none of the particle components could be definitely excluded as having health effects, thus supporting the current regulatory approach of targeting the entire PM mix. Yet, given the varied approaches that can be, and are, used to control emissions from different sources, interest remains high in source contribution (and composition) to toxicity of PM. Interest also remains very high in other characteristics of PM, particularly size.

- Air pollution sensors that are less expensive than traditional regulatory- or research-grade monitors offer the promise of improving exposure assessment of outdoor air pollution. Given their lower cost, such sensors are being widely used by individuals and deployed by community and other organizations to learn about their local or individual exposures. Two main concerns here are first, obtaining data of sufficient quality is hampered by the rapidly changing nature of the technology and the fact that the influence of temperature, humidity, and other conditions becomes important when sensors are deployed in environments that are not climate-controlled and are used for extended periods of time. And second, information on the risks of air pollution is based on population-level studies, and it is very difficult to translate exposure information to local or individual risks.

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

Health Impact of Exposure to Low Levels of Air Pollutants:

- HEI will complete, within the first years of the new Plan, its health effect studies of low-level exposure, applying innovative exposure and analysis techniques, examining PM, ozone, and NO_2 effects at low ambient levels, in the United States, Canada and Europe. HEI's path breaking program of these major studies in millions of participants will produce important new findings that will inform EPA decisions on National Ambient Air Quality Standards (NAAQS) and WHO decisions on Global Air Quality Guidelines, as well as future estimates of benefits from air pollution reductions. These studies will also pave the way for novel methodologic advances in air pollution studies for years to come.

These unprecedented efforts to gather comprehensive information on tens of millions of participants and their exposure will provide opportunities to apply the same or similar methods for exposure assessment for comparison among the different studies, best ways to address confounders and measurement error, and other analytical approaches, including methods for causality inference. Additional questions that may be pursued include multi-pollutant analyses methods and PM composition or source analyses, methods developed for one cohort and tested in another, sources of variability in effects in the various populations such as age structure, SES position, and access to medical care, to name just a few.

Studies on the Mechanisms of Health Effects of Low Level, Chronic Exposure

- The observation of associated health effects in early epidemiology analyses in low exposure studies raise questions of the biological/toxicological mechanisms that may operate under chronic, low exposure conditions. Though toxicological and mechanistic confirmation of effects is not essential for reliability of epidemiologic observations, such consistency of evidence is strong, supportive evidence for plausibility (and can even contribute to causality). How might these questions be addressed? HEI could, through workshops and exploratory studies, investigate the best ways to research these mechanistic questions and is eager to hear comments and ideas on promising directions that HEI might pursue.

- Another area with a need for research on the mechanisms of chronic exposures at low levels relates to the health effects of ozone where epidemiological studies have shown associations with cardiovascular mortality but where results of ozone exposure in chamber studies have generally – especially at low levels – not found effects. This may point to the need for new approaches to mechanistic studies, and application of novel methods. Here too, HEI would welcome comments and ideas on scientific activities that HEI might consider.

Characteristics and toxicity of PM

- There continues to be intense interest, and potential policy payback, regarding whether any specific characteristic of PM confer differential toxicity, which could lead to actionable control strategies. Embedded in this issue are questions regarding sources of PM (e.g., mobile vs stationary sources, and also biogenic sources, and chemical composition), size characteristics (e.g., ultrafine, and coarse particles, and features of size, such as diameter vs surface area, surface charge or other features), nature of PM (e.g., freshly emitted PM, SOAs, aged PM), and many others. Given that epidemiological studies on such questions are very difficult and past studies have not provided clear cut answers, should HEI take a renewed look at these questions? What approaches and developments in toxicology may be most useful for such applications?

Transport and Urban Health

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

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

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

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

A First Step – the Updated HEI Traffic Review

Under the current Strategic Plan, HEI's new Expert Panel on the potential health effects of exposure to traffic is actively engaged in reviewing the literature published since HEI's earlier review in 2010. Since that time, over 1,000 studies of traffic exposure and health have been published. The new Panel is systematically screening and evaluating these studies, with an emphasis on studies of long-term effects. This effort, which is expected to be completed around the end of the first 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. 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. Importantly for HEI's *Strategic Plan 2020 – 2025,* this new review should also – much as its predecessor did – set the stage for the highest priority further studies to be tackled under HEI's new Plan.

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

The HEI *Strategic Plan 2020 – 2025* will provide an opportunity to learn from HEI's newest studies of traffic, which were designed and implemented in the wake of a series of HEI studies to enhance the assessment of traffic exposure for use in epidemiologic studies (a key recommendation of HEI's earlier traffic review). These new studies, underway currently and likely to be reviewed and

published near the middle of the new Strategic Plan, are incorporating improved traffic exposure approaches but also, importantly, considering other key factors found in the urban traffic environment that may also influence health. These factors include noise, socioeconomic status, and access to green space, for which there are separate literatures suggesting potential effects, that may modify or confound the effects of traffic air pollution exposure, and examining them all together should enhance our understanding of their roles in urban health.

At risk Populations

A not insignificant part of the interest in recent enhanced monitoring of roadside air pollution exposures is the disproportionate representation in roadside populations of environmental justice communities, i.e. populations of lower socioeconomic status and often peoples of color who may have inadequate medical care and/or other underlying health challenges which may raise their sensitivity to the health effects of air pollution. Also potentially of concern are populations in these settings with certain underlying diseases that can increase sensitivity to the exposures (e.g. asthmatic children and adults, and those with diabetes). In addition to the three new studies above of traffic exposure, socioeconomic status, and other factors, HEI is supporting an additional study in New York (by **Jane Clougherty**) exploring these issues of disproportionate exposure and effects and a separate microscale assessment of traffic exposures in urban settings (by **Josh Apte**). Should the early findings of this group of studies support it, HEI would, in a new Plan, enhance its efforts to probe this important set of questions.

Exposure Components of Special Interest

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

- *Ultrafine particles:* HEI's 2013 Perspectives *Understanding the Health Effects of Ambient Ultrafine Particles* summarized current science on exposure to and health effects of ultrafine particles, and concluded "The current evidence does not support a conclusion that exposures to UFPs alone can account in substantial ways for the adverse effects that have been associated with other ambient pollutants such as $PM_{2.5}$." A recent review conducted for the German Umweltbundesamt (the German EPA) reached similar conclusions. These reviews also identified a number of continuing research needs – and questions continue to be raised about ultrafines potential role in effects observed in traffic exposure studies, especially because it seems likely that some new technologies being introduced in the market, such as gasoline direct injection (GDI), emit UFPs. This set of issues is likely to continue to be of importance as decision makers in the US and globally consider what if any action to take on particle number standards for light duty and heavy-duty vehicles in light of the European action in this area. HEI is inviting new exposure studies to better characterize long term exposures to harder to assess air pollution components such as ultrafines (RFA 19-1); we would welcome input on this draft plan on the priority of further research in this area, and which areas should draw the greatest attention.
- *Non-tailpipe Emissions:* With a significant reduction of tailpipe PM emissions from gasoline and diesel vehicles, interest in non-tailpipe emissions of motor vehicles is increasing, and there is interest in understanding how the non-tailpipe emissions could affect exposures of individuals living near major roads. Since relatively little work has been done on such emissions, HEI has initiated some research to characterize these exposures and their potential effects. Understanding these exposures is not, however, always straightforward and continued attention to improving exposure assessment is needed. HEI would also welcome input on the priority for, and directions in, this research area under the new Plan

- *Increased use of Low Carbon and Biofuels*: As one element of a transition to lower vehicle greenhouse gas emissions, efforts to increase use of low carbon fuels are continuing. While these fuels offer an opportunity for cleaner emissions, they may also introduce new chemical compounds into the fuel mixture and combustion process, with a wide variety of potential effects on emissions. HEI has continued to track these questions over the current Strategic Plan, with a major multi-party expert workshop convened in Chicago in 2016 and monitoring of the latest science. 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 track technical developments, and 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 EPA and industry sponsors, WHO, the EU and others affecting public health, technology and potential regulation. This science also helps inform regulatory decisions in developed countries that are then transferred to the developing world (e.g. EURO vehicle standards)

HEI's future work in developing Asia and beyond, with supplemental support, will enable HEI to provide much needed credible science to inform decisions in parts of the world with some of the very highest levels of air pollution on the planet. To do this HEI will work in partnership with leading global research institutes and investigator teams employing cutting edge satellite data, multi-scale atmospheric models, ground-based monitoring, and the growing base of health studies in many countries, often in a capacity building relationship with local scientists. This approach, and HEI's careful communication to decisionmakers builds trust and provides unique traction for results that fosters the reliance on high quality consistent science for local decisions.

Europe and the Developed World

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

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

- Studies of major pollutants ($PM_{2.5}$, ozone, NO_2, CO, and some air toxics)
- Studies of low-level effects of air pollution
- The health impacts of exposure to traffic related air pollution
- Studies of ultrafine particles and advanced technology internal combustion engines

This and related research will help inform consideration of European limit values, emission ceilings, vehicles and other emission standards, and national and city level decisions about traffic control and related interventions. In turn, these decisions will provide guidance to many countries in the developing world.

Developed Asia and Beyond

In developing Asia and beyond, as reported in SoGA 2019, air pollution and associated mortality and morbidity continue to increase in many areas, 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 vehicle ownership and miles traveled, electrification and industrial activity. While growth will bring many benefits in improved socio-economic status, and declines in solid fuel use, developing nations will be hard pressed to reduce air pollution and associated CO_2 emissions in the near term. In this context understanding the health impacts of key sources will be critical to help guide health relevant interventions in nations with limited resources.

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

Global Burden of Disease: HEI will continue to work with IHME, providing leadership on the air pollution working group to update both health and monitoring data, refine methods to estimate exposure response, and evaluate additional health endpoints and pollutants for inclusion in GBD 2019 and beyond

GBD-MAPS Global: Identification of contributing sources and their relative health impact is important to address air quality management at the national and sub national level. HEI proposes to build on its earlier GBD MAPS China and India studies by using global emissions inventories by country and sector combined with advanced modeling and updated integrated exposure response functions to build GBD-MAPS Global, a report on source-specific air pollution health impacts for all countries in the world. As in Asia, this data is expected to aid health-based air quality management in countries with limited ability to acquire this information, and when combined, provide a comprehensive global analysis of key sources, effects and trends. This will also enable, over time, the projection and tracking of changing sources as economies grow and evolve, e.g. shifts in main power sources, and expected growth in vehicle fleets.

State of Global Air: HEI will maintain and enhance its annual State of Global Air Report and database. This will enable continued identification and tracking of key progress and trends in global air pollution, beginning in 1990 through the current year, assessing levels of $PM_{2.5}$, and ozone, and the health impacts of ambient and household air pollution, including measures of life expectancy on global health. It will also provide an accessible and transparent mechanism for tracking progress in improving air quality.

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 a subset of key studies are needed in developing nations to credibly inform extrapolation to this body of existing science to national conditions. In addition, there is a dearth of studies of chronic exposures in Asian populations that would be informative in refining estimates of health impacts in these same populations. Under its new Plan, HEI plans to complete, peer review and publish the Asian cohort studies being undertaken by Vermeulen et al and, with supplemental support, HEI will identify and report on key gaps in the air pollution literature in developing Asia and seek to support studies to fill those gaps, pursuing a capacity building model designed to enhance both the skills of local scientists to conduct such research in the future and produce results with maximum credibility to local officials.

Cross-Cutting Issues

In reviewing these detailed major opportunities that HEI might address going forward, a number of specific health effects questions were identified that would not by themselves be programs of research in the new Strategic Plan, but which should be viewed as *cross-cutting issues* that should be integrated into all of HEI's work. Several issues were included in the Strategic Plan 2010-2015 but remain pertinent for future research:

Transparency in Policy-Relevant Science

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

HEI does not plan to engage in direct research or consensus building in these areas; however, these issues do intersect with HEI's research and review activities and we envision engaging in the following ways.

Data Access and Transparency are essential to the scientific process because they can provide insight into analytical and methodological details. Making data and analytical methods available allows others to replicate study results independently and, where necessary, perform alternative or additional analyses. As such, transparency provides equally valuable feedback to the decision-making process. Taken together, both accountability and transparency underscore HEI's commitment to improving science for regulations.

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

During Strategic Plan 2020-2015, HEI plans to continue its involvement in this area, by making data from studies it funds widely available for reanalysis, replication, and extended analysis by others. Specifically, as discussed above under Accomplishments, HEI will work with the investigators of the low-level exposure and its other studies to make their data and codes available.

Systematic Synthesis of Information on Important Issues. Using special expert panels and its scientific committees, HEI has long played an important role in collecting, analyzing, and synthesizing scientific information on important issues facing the EPA and its private sector sponsors. This has taken the form of special reports and perspectives developed by special expert panels and staff. The most recent examples of such activities include a major review of the traffic

literature (2010), ultrafine particles (2013), diesel epidemiology studies among miners and truckers (2015) and new technology diesel engines (2017).

The process for performing and synthesizing reviews has been evolving and currently the use of *systematic* review protocols has been emphasized in the environmental health context. However, it is also becoming clear that such protocols – often derived from clinical trials literature – are not well suited for the observational epidemiology literature. The HEI panel reviewing the health effects from exposure to traffic related air pollution is currently working to adapt procedures for its review work. The Panel's protocol will be published in summer 2019 at the PROSPERO website (https://www.crd.york.ac.uk/prospero/), and the review using these procedures will be published early during the new Plan.

Analysis for Causality. HEI's work in this area is, by and large, integrated into other HEI research to develop statistical and analytical methods. In these areas HEI has played two key roles: to *develop innovative methods*, and then to *test and validate those methods* to ensure that they provide high-quality information for better understanding and decision making. Looking forward, there are several key opportunities for incorporating innovation and validation in all aspects of HEI's work, including

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

Enhanced Exposure Assessment

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

To that end HEI has some new activity just beginning under a new Strategic Plan, and is considering additional areas where HEI might engage during the course of the Plan:

- First, as discussed above, HEI has recently issued an RFA seeking to fund studies to advance exposure assessment for air pollution and health studies using sensors, mobile monitoring, tracking technologies, and other approaches. The studies would develop and apply novel approaches to improve long-term (months to years) exposure assessment of outdoor air pollutants whose levels vary greatly in space and time, such as UFPs, NO_2, and components of PM.

- 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 growing field and, as needed, identify specific efforts it might undertake to evaluate and enhance these techniques.

- Third, as noted under Transport and Health above, there are a number of components of the transport exposure mix which continue to attract attention for their potential shorter-term exposures and effects. HEI will continue to monitor these issues and identify roles that HEI might play in improving assessment of these exposures.

HEI would welcome comments and ideas on other exposure issues and research questions that HEI should be focusing on.

Sensitive and at-Risk Populations

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

New methods for toxicity testing, mechanisms and biomarkers

HEI will also encourage in its research programs the use of new methods, model systems, and systems biologic approaches for toxicity testing, mechanisms and biomarkers, with the goal of improving exposure and dose-to-target tissue assessment, genetic or epigenetic factors affecting susceptibility, and species specificity. HEI is interested in studies focused on mechanisms of action, especially as they pertain to enhancing our understanding of species- or dose-related extrapolations or early markers of pathologic outcomes and may help identify biomarkers. Although many other groups at the EPA, National Institutes of Health, and elsewhere are developing such techniques, HEI will use its unique position to apply and test these techniques in challenging areas.

HEI sees several areas where the new methods may be particularly fruitful. First, in view of the increasing deployment of new fuels and technologies and the paucity of information about the health effects of their emissions, such methods will be particularly useful in the development of more reliable and cost-effective screening tools. Second, as discussed above, HEI is interested in exploring and potentially applying such new methods to study the effect of chronic exposure to low levels of air pollutants. Finally, although scientists have searched for biomarkers for a long time, advances in proteomics, genomics, systems biology, immunology, neurobiology, understanding of gene-environment interactions, and advances in various measurement methods raise anew the possibility that biomarkers may be found for certain pollutants, and these advances have the

promise of providing more reliable methods for dose or exposure assessment and early markers of disease. HEI will encourage the investigators it supports to propose such approaches in their research, ideally side by side with more traditional and well-validated approaches, to build a broader "tool box," for assessing exposure or health effects.

CHOOSING THE FUTURE

HEI has already begun to receive much valuable input from sponsors and others in putting forward the potential directions for the *HEI Strategic Plan 2020 – 2025* described above. As we go forward, and get comments on this draft of the Plan, HEI staff and committee members will address several criteria in selecting priority topics for the next five years. These include:

- the current state of knowledge about topics of potential interest,
- their importance for upcoming regulatory and technology decisions,
- how well they are being addressed by other organizations, and
- the likelihood that additional scientific work will produce useful findings at this time.

Figure 7 illustrates this process. In appraising how each of the possible directions addresses these criteria, HEI will also consider its ability to provide science to inform both near- and longer-term decisions, and the overall resources available to HEI to produce its science.

Figure 7. Choosing the Future