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Aaron Yeow, M.P.H.
Designated Federal Officer
U.S. Environmental Protection Agency
Science Advisory Board
1200 Pennsylvania Avenue, NW (1400R)
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Dear Mr. Yeow:

The Health Effects Institute (HEI) is pleased to respond to the questions you have forwarded to us about HEI's Accountability Research Program from Dr. Anthony Cox, Chair of the Clean Air Scientific Advisory Committee (CASAC). As we noted in our testimony on the PM ISA there are a broader set of tools that can be applied to determine causality drawing on all lines of human and laboratory evidence, but we do view accountability research as a valuable opportunity to test causality in real world settings.

1. *Could HEI provide a list of all reports they have published on accountability studies for PM2.5, and any that are now in the pipeline? For the ongoing studies, do you have estimated completion dates?*

HEI, at the request of our sponsors in industry and at the US EPA, initiated this new program in Accountability research – attempting to test the effects of air quality interventions on air quality, exposure, and health – in 2003 with a first expert monograph (HEI Working Group 2003). We then proceeded to fund competitively a series of over a dozen such studies, all of which were focused along the "Accountability Chain" illustrated in Figure 1.

These studies, which are described in the attached Table 1, and referenced in the attached list of references, spanned a range of types of studies including studies of:

- Short-term interventions (e.g. to reduce air pollution during an Olympics)
- Interventions designed to control a specific source (e.g. household coal and wood burning; power plant control programs, fuel switches)
- "Natural Experiments" (e.g. air quality and health changes from the reunification of Germany), and
- More comprehensive ranges of interventions designed to reach attainment of air quality standards under the US Clean Air Act.

During the course of these studies, as initial results came in and were reviewed for publication by HEI, HEI conducted two detailed workshops and published further guidance on new directions (van Erp and Cohen 2000, HEI 2010). These in turn led to new Requests for Applications and second and third waves of studies. Most recently, HEI issued a new *RFA 18-1: Assessing Health Effects of Air Quality Actions at the National, Regional, and Local Levels* (attached) to identify major new opportunities for studies; these studies are expected to get underway in late 2019 and early 2020.

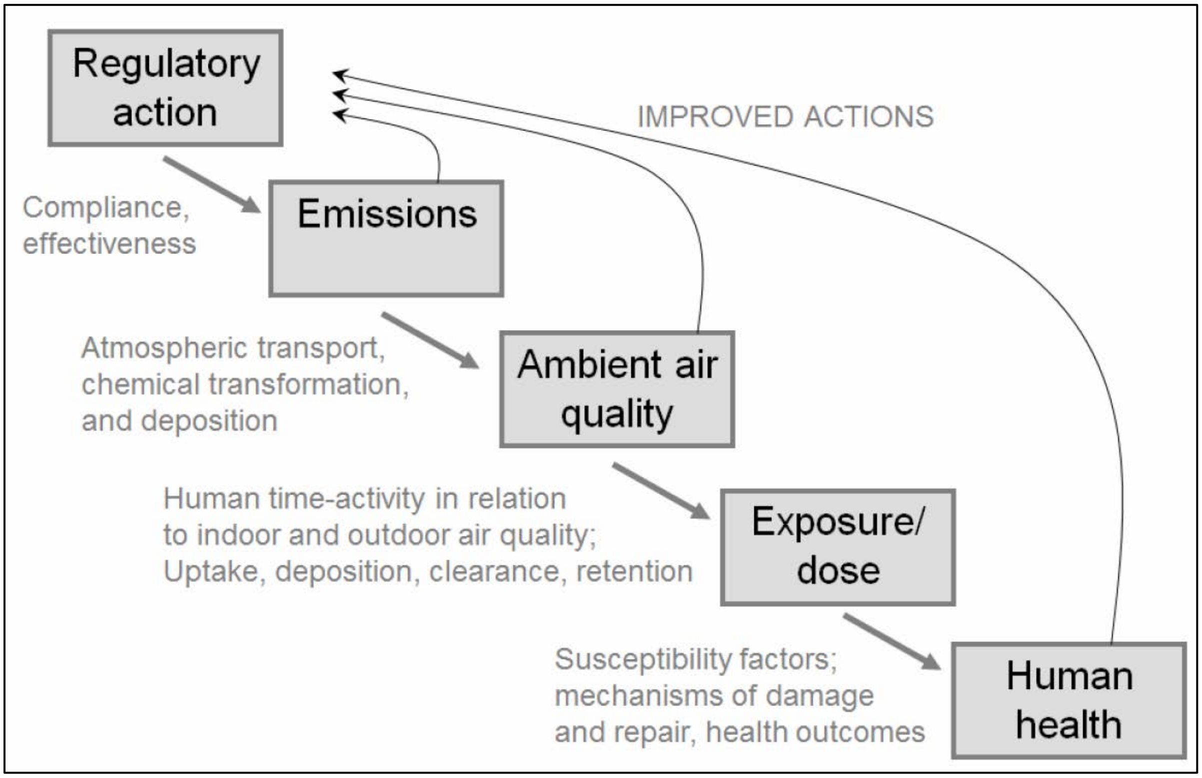

Figure 1. The Chain of Accountability

2. *What is HEI's current understanding of the state-of-the-art in what has been learned so far from accountability studies of PM2.5? To your knowledge, have accountability studies been completed from which it is possible to obtain quantitative estimates of the increases in life expectancy or decreases in all-cause or cause-specific mortality or morbidity rates caused by the independent direct effects of reductions in ambient PM levels?*

HEI has not itself conducted a systematic review of all of the Accountability literature, but leading HEI scientific staff did publish a summary and evaluation of all of the current HEI-funded studies (Boogaard et al 2017). That review identified the significant progress that has been made in developing and applying new and robust analytic techniques in increasingly complex regulatory situations – and identified lessons learned that helped inform the new HEI RFA 18-1. In addition to this review, two other useful reviews of the broader literature (including HEI studies) have been published by Rich (2017) and Henneman et al 2017). These draw similar conclusions concerning the state of the art, the increasing sophistication of the studies, and the need for enhanced data and analysis techniques going forward.

Although this body of research is still in development, one can highlight several key findings to date:

- Although none of the studies has been designed specifically to provide the quantitative estimates mentioned in the question, many of them do take advantage of the clear temporal variation in exposure before and after an intervention to determine – even while minimizing and/or eliminating potential sources of confounding – that the interventions resulted in clear and quantifiable changes in air pollution and different measures of health outcomes. For example, the most recent study published by HEI (Russell 2018) was able to analyze the substantial improvements in air quality accomplished by a range of mobile and stationary interventions in the Atlanta area, especially when comparing current levels to those that would likely have occurred in the absence of intervention (i.e. the counterfactual). In turn, they were able to apply those changes to determine quantitative estimates of prevented emergency department visits, especially for asthma and other respiratory outcomes.

- The HEI studies have also identified several important accountability research design elements that – if absent – can lead to misleading results. For example:

  - Careful analysis of the link between the regulatory action, reductions in emissions, and ambient air quality is necessary. In the HEI-supported, more comprehensive, analysis of the traffic interventions around the Atlanta Olympics (Peel 2010), detailed analysis of the actual traffic volumes before, during, and after the interventions showed little reduction. Also, the ozone reductions seen in Atlanta during the games (Friedman 2001) also occurred throughout the Southeast, in areas not affected by the traffic changes, likely a result of meteorology.

  - The systematic comparison of other time-varying trends can influence whether a health benefit is seen from an air quality intervention. When Dockery et al (2013) reanalyzed their earlier study of effects from the banning of household coal burning in Dublin, Ireland (Clancy 2002) – and extended it to other cities where bans had been enacted – they also analyzed health outcomes for cardiovascular and respiratory mortality in a group of "comparison" counties that had not implemented any change in coal use or seen reductions in air pollution. Use of this comparison found that:

    - There was no difference in cardiovascular mortality between those counties that did see an air quality improvement and those that did not, suggesting that other factors in cardiovascular care (e.g. new drugs and treatments) were responsible.
    - *However,* they did observe a measurable benefit: improvement in respiratory mortality in the improved air quality locations compared to the comparison counties.

  - The studies illustrate that it can be possible to determine the effect of a source-specific intervention on air quality in some circumstances – e.g. the replacement of all wood stoves in Libby, Montana with cleaner burning stoves (Noonan, 2011). However, it is more difficult to determine which specific interventions may be responsible for the significant improvements in the case where a range of significant actions have resulted in measurable air quality improvements (e.g. Southern California (Gilliland 2017), Atlanta (Russell (2018)). This does not affect the ability to test whether overall improvements in air quality can be causally linked to health improvements (they can be), but rather makes the determination of which specific intervention may be most effective more difficult.

In closing, we hope these studies provide a key element of the broader evidence to determine the effects of air pollution – and stand ready to provide whatever additional information you might find useful, or to answer any further questions that CASAC might have.

Sincerely,

/s/

Dan Greenbaum
President

Attachments:
References
Table 1. HEI Studies
RFA 18-1: Assessing Health Effects of Air Quality Actions at the National, Regional, and Local Levels

References

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Table 1. Overview of accountability studies funded by HEI (listed by funding date)

Intervention	**Study Design / Period**	**Citations**	**Major Strengths and Challenges**
Ban on sale of coal in Dublin (1990) and other cities in Ireland (1995, 1998, and 2000)	Retrospective time-series; 1981-2004	Clancy et al. 2002 (original study) Dockery et al. 2013 (follow-up)	Included comparison populations presumably unaffected by the intervention. Confounding by long-term background trends for total and cardiovascular mortality.
Switch from brown coal to natural gas for home heating and power plants, changes in motor vehicle fleet after reunification of Germany	Retrospective time-series; 1991-2002	Peters et al. 2009	Innovative methodologic work on how risk estimates varied over time. Limited statistical power due to small population size.
2003 congestion charging scheme in London	Emissions modelling and air quality evaluation; 2001-2005	Kelly et al. 2011	Use of a variety of multidisciplinary approaches. Small target area (inner city), and regulation not targeted at air quality per se; confounding by regional background pollution; unintended consequences.
2008 low emission zone in London	Collection of baseline air quality and health data before LEZ went into effect	Kelly et al. 2011	Additional road-side monitoring. LEZ implementation was taking place in stages over multiple years; air quality improvement was expected to be fairly gradual.
1990 Clean Air Act Amendments to restrict power plant emissions of NOx and SOx in the Eastern U.S.	Statistical analyses linking emissions and source-receptor data; 1999-2005	Morgenstern et al. 2012	New statistical approach and use of counterfactual scenarios. Large uncertainty in models due to large number of variables and missing data, and potential application remains unclear.
Wood stove change-out in Libby, Montana during 2005 – 2007	Prospective study in school age children, parent questionnaire; 2003-2009	Noonan et al. 2011	Successful change-out program with 95% of stoves replaced. Prolonged time frame of the intervention, small size of population, and use of limited health survey data.
Traffic restrictions during 1996 Olympic Games in Atlanta, Georgia	Retrospective time-series; 1995-2004	Friedman et al. 2001 (original study) Peel et al. 2010	Evaluated seasonal changes in surrounding years and included comparison locations Short duration of the intervention; limited statistical power.

		(follow-up)	
1990 sulphur restrictions in fuel in Hong Kong, China	Retrospective time-series; 1985-1995	Hedley et al. 2002 (original study) Wong et al. 2012 (follow-up)	Evaluation of PM components and innovative statistical approach to assess life expectancy. Inability to disentangle the effects of individual pollutants; confounding by long-term background trends.
Industrial emissions and traffic restrictions during 2008 Olympic Games in Beijing, China	Prospective panel study; before (June 10–July 6), during (August 4–29), and after (October 6–31)	Zhang et al. 2013	Strong prospective design. No comparison populations; unclear clinical significance of changes in biomarkers in healthy subjects.
Numerous air quality regulatory policies and emission reduction strategies in California	Children's Health Study cohorts; 1993-2012 (includes 3 cohorts)	Gilliland et al. 2017	High quality exposure and health data over two decades. Complex sets of regulations; link to specific air quality regulations was largely descriptive, unexplored variability in the relationship between changes in air pollution and respiratory health among the communities.
2006 California Emission Reduction Plan for Ports and Goods Movement	Retrospective cohort study; 2004-2010	Meng et al. 2017 (conference abstract)	Detailed exposure assessment before and after the intervention, and inclusion of control areas. Implementation was gradual.
Various complex long-term regulations targeting power plants and mobile sources in Atlanta, Georgia	Emissions and air quality modelling linked to time-series approach; 1993-2012	Russell et al. 2018	Development of counterfactual scenarios and a rich air quality and health database. Health estimations were based on standard burden and risk assessments methodologies.
PM10 nonattainment with NAAQS and installation of SO2 scrubbers on power plants in the US	Statistical methods development	Zigler et al. 2016	New causal modeling methods for accountability research. Regulations may also affect air quality and health in neighboring counties treated as "controls".

RFA 18-1: ASSESSING IMPROVED AIR QUALITY AND HEALTH FROM NATIONAL, REGIONAL, AND LOCAL AIR QUALITY ACTIONS

INTRODUCTION

The Health Effects Institute (HEI) is seeking to fund research to assess the health effects of air quality actions, also known as *accountability* research. Accountability research refers to empirical studies assessing the effects of regulatory actions, other interventions, or "natural" experiments on air pollution and health (sometimes also referred to as intervention studies). Request for Applications (RFA) 18-1 solicits applications for studies designed to assess the health effects of actions to improve air quality and to develop methods required for, and specifically suited to, conducting such research. Areas of interest include, but are not limited to:

(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;

(4) **Methods development and dissemination:** studies that develop, apply and disseminate statistical and other methodology for conducting such research.

RFA 18-1 is a continuation of efforts by HEI and other organizations to conduct accountability research, which is of ever-increasing interest. HEI Communication 11, Assessing Health Impact of Air Quality Regulations: Concepts and Methods for Accountability Research (HEI Accountability Working Group 2003) set out a conceptual framework for assessing the health effects of air quality actions, identified the types of evidence required by the framework, and described the methods by which that evidence can be obtained. Based on that framework, HEI has funded an extensive program of thirteen studies to date. In addition to the concepts outlined in Communication 11, various publications by HEI and others have summarized the results, challenges encountered, and lessons learned and have provided possible directions for future research (e.g. van Erp and Cohen 2009; Health Effects Institute 2010; Henschel et al 2012; Hubbell 2012; Pope 2012; van Erp et al 2012; Boogaard et al 2017; Henneman et al 2017; Rich 2017). These publications have informed the development of the current RFA.

HEI expects to make available approximately $6 million for this RFA and to fund up to 4 larger studies (3 to 4 years in duration, maximum budget $1.2 M) and 1 or 2 smaller-scale methods development studies (2 to 3 years in duration, maximum total budget $700,000).

BACKGROUND

Interest in assessing the health outcomes of air quality actions has grown in response to questions about the benefit of tightening air pollution regulations. Since the 1980s, measurements at thousands of monitoring stations across the United States have shown reduced concentrations of all six criteria pollutants. This progress is, of course, associated with a price. The U.S. Environmental Protection Agency (EPA) estimated that from 1970 to 1990 the direct cost of air pollution control was about $25 billion per year — more than $500 billion over 20 years. Even as new research has strengthened evidence for both adverse health effects due to air pollution and the case for regulatory and other preventive measures, and even as estimates of health benefits have found that the estimated benefits exceed the estimated costs (Office of Management and Budget 2017), policy makers, legislators, industry representatives, and the EPA continually seek to document whether past efforts to reduce air pollution have yielded demonstrable improvements in public health and to better predict whether future efforts will continue to do so. In particular, it will be important to know whether health benefits can be observed of pollution reductions at the relatively low levels currently attained in the US. In addition, interest in assessing the health effects of air quality actions intersects with a growing appreciation among stakeholders and the scientific community of the need to evaluate the health outcomes of actions taken to slow climate change (e.g., Smith et al 2009) that may provide co-benefits. More recently, interest in accountability has expanded globally due to high air pollution concentrations in Asia and elsewhere, and fast-paced efforts to improve air quality in those regions (in particular in China) to reduce the substantial burden of diseases associated with ambient air pollution arising from both indoor and outdoor sources (GBD MAPS Working Group 2016, 2018; Huang et al 2018).

National governments and public health agencies have attempted to quantify past health benefits of air quality improvement and to estimate future health effects. These assessments have generally relied on risk estimates from epidemiologic studies to calculate public health outcomes under air quality scenarios that reflect either the continuation of past exposure patterns or future exposure patterns assuming more stringent air pollution control (Environmental Protection Agency 2011). However, such estimates need to be validated by comparison with results of "real world" studies of regulatory programs and other actions using actual health outcomes data. Due to the considerable challenges inherent in such research, the number of studies undertaken to date remains limited although it has been growing (as reviewed recently by Boogaard et al 2017; Henneman et al 2017; Rich 2017; Burns et al in press). Although some studies have contributed to statistical methods development in this area (e.g. Harrington et al 2010; Zigler et al 2016), further development of suitable epidemiologic and statistical approaches remains important to support the evaluation of air quality actions.

Accountability studies typically compare air quality and/or population health before and after implementation of an air quality action, although they often defy a clear study design classification. Accountability studies are appealing since they are the closest epidemiologic equivalent to controlled experimental studies in the field of air pollution research, and thus may provide evidence to support the assessment of causal relationships. This apparent advantage does not imply, however, that accountability studies are less susceptible to confounding factors that may bias the results.

Efforts to measure the consequences of air quality actions remain challenging. Air quality actions do not exist in a vacuum; often multiple interventions are implemented within the same time frame and at multiple levels (e.g., national, state, and local). Diverse approaches are therefore needed to evaluate the outcomes of these actions on a variety of temporal and geographic scales. The consequences of interventions may also lead to other, sometimes unintentional, changes. For example, whether or not an intervention improves air quality, it may result in behavioral changes, or in economic activities (or other factors) that may affect health. Therefore, it may be difficult to isolate whether the air quality action reduces air pollution concentrations and subsequently improves health. Ensuing changes in emissions, ambient concentrations, and human exposure may not be demarcated sharply in space or time, and the dynamics of biological processes of injury that underlie adverse health effects of air pollution may not immediately follow the changes in exposure that result from air quality action but may have a latency period of months to years. The longer the time between promulgation of a regulation and its effects, the greater the possibility that other factors that influence air quality and health outcomes (e.g., an economic downturn, demographic changes, changes in medical practices, and access to health care) may come into play and interfere with demonstrating the effects of the intervention itself. The degree to which the regulation is enforced may further complicate the analysis by extending the anticipated time between intervention and effect.

HEI Communication 14 (van Erp and Cohen 2009), Communication 15 (Health Effects Institute 2010) and various other publications by HEI and others (Henschel et al 2012; Hubbell 2012; Pope 2012; van Erp et al 2012; Boogaard et al 2017; Henneman et al 2017; Rich 2017) have summarized the results of accountability research, the challenges encountered and lessons learned, and have provided possible directions for future research. The key challenge in accountability studies is to disentangle policy-related changes in air pollution and health from other time-varying factors influencing air quality and/or health (see e.g. Dockery et al 2013; Gilliland et al 2017).

Early studies of the health effects of air quality improvement programs implemented over short time frames (e.g., a ban on the sale of coal in Dublin, see Clancy et al. 2002; Dockery et al 2013) as well as natural experiments (e.g. the temporary closure of a steel mill [see Pope 1989] or coal-fired power plants [Russell et al 2017]) suggest that the outcomes of such interventions may be directly measurable after a relatively short time period if a substantial change in air quality is produced. However, other studies, most notably of interventions aimed at reducing traffic congestion, have found only small improvements in air quality that hamper evaluation of health effects due to lack of statistical power (Kelly et al. 2011a), or have found that the observed air quality changes were regional in nature and could not be definitively related to the intervention at the local level (Peel et al. 2010). In recent years, many cities have started to take actions at the local level to improve air quality, for example by creating low emission zones, congestion charging, or banning diesel vehicles. Additional research is needed into the effectiveness of these traffic measures and other actions at the city level; rapid changes in urban transportation and measures to make cities more livable may provide other opportunities for such research.

OBJECTIVES OF RFA 18-1

1. Fund empirical studies to assess the health effects of air quality actions (regulatory and other air quality interventions as well as natural experiments). Areas of interest include, but are not limited to:
   a) National- or regional-scale regulatory actions implemented over multiple years;
   b) Local actions targeted at improving air quality in urban areas, with well-documented air quality problems and programs to address them;
   c) Regulatory programs to improve air quality around major ports and transportation hubs and corridors; and
2. Develop methods required for, and specifically suited to, conducting such research; and make those methods accessible and available to other researchers.

RFA 18-1 seeks proposals to assess the health effects of air quality actions. Areas of interest are defined below but are not limited to those because real-world opportunities available for evaluation may be relatively scarce. Air quality actions include regulatory actions, other interventions, or “natural” experiments (e.g. major public or private actions not designed to improve air quality but that are likely to result in reduced air pollution levels; it includes unintentional events, such as factory closures or economic downturns, as long as researchers can justify that the air quality changes are large enough and last long enough to study). Thus, HEI’s interests include studies of regulatory or other public actions implemented for goals other than improving air quality, for example to reduce climate-related emissions, to close major transportation hubs or other air pollution generating facilities, or traffic congestion. Studies evaluating the effects of general improvements in air quality on health, without any formal linkage to specific air quality actions, will not be considered responsive. Studies that evaluate economic consequences or do not have a health component will also not be considered responsive. Studies evaluating interventions to reduce personal exposure (e.g. use of face masks or in-home air filters) are not within the scope of this RFA.

As indicated in the HEI Strategic Plan 2015-2020 (Health Effects Institute 2015), applicants are encouraged to (1) focus on health outcomes that are well-justified and for which evidence of a link with air pollution has been reasonably well-established, (2) consider disadvantaged and susceptible populations in their proposed research, (3) identify whether their study design can contribute to the evidence regarding causal relationships between air pollutant exposures and health outcomes, and (4) contribute to the scientific knowledge base in addition to conducting an air quality action evaluation.

Proposed studies should document in detail the measured or projected effects of specific interventions or groups of interventions on emissions and ambient concentrations in order to demonstrate that a considerable enough change has occurred (or is expected to occur) to have the potential to produce a measurable change in human exposure and effects and to allow for assessment of changes in health outcomes (see *Critical Study Design Considerations* below). This is particularly true for smaller-scale, local interventions.

Studies with prospective as well as retrospective designs will be considered; however, HEI specifically encourages investigators to submit proposals for prospective studies, in particular when evaluating local actions. The RFA does not target specific health outcomes as long as they have been sufficiently linked to air pollution exposure in previous work. The RFA welcomes proposals from around the globe, including China, and other low and middle-income countries with demonstrated commitment to major air quality interventions, as long as they meet the criteria specified in this RFA.

Ideally, accountability research would be incorporated into policy development. This process may include an iterative cycle of prospective and retrospective analysis, whereby potential outcomes of policies are evaluated using exposure and risk assessment models during the initial policy development phase, and the results of policies are evaluated once air pollution reduction strategies have been implemented. Investigators are encouraged to consult with government agencies and also with local communities to look for opportunities to incorporate accountability research at an early stage. Any study planned in this fashion will need to assess the availability of high-quality data on baseline conditions of air quality, exposure, and health for comparison against post-intervention measurements. We refer applicants to recent HEI-supported efforts in this area (e.g. Gilliland et al 2017; Russell et al 2018).

The following sections outline specific areas of interest targeted under this RFA, as specified in the objectives, as well as general study design considerations.

1. Studies to Assess the Health Effects of Air Quality Actions at the National, Regional, and Local Levels

1a. National- or Regional-Scale Air Quality Actions Over the Long Term

In the United States, over the past decades the EPA has been implementing a number of major regulatory actions, including the on-road and off-road diesel rules, rules covering locomotives and marine vessels, National Emission Standards for Hazardous Air Pollutants (NESHAP) standards for utilities and industrial boilers, and the Cross-State Air Pollution rule (CSAPR). Individual states and regions are also implementing and planning regulations covering a number of important sources of air pollution, including actions to reduce emissions in major ports and transportation corridors (California Air Resources Board 2006; National Environmental Justice Advisory Council 2009).

Other countries across the globe have been implementing similar national or regional scale air quality action plans. The European Union has rolled out its Clean Air for Europe program (European Commissions 2018). In Asia, China in particular is taking steps to address the high air pollution levels in its major cities. HEI is interested in research proposals that evaluate air quality actions over the entire range of exposure concentrations, including low as well as high concentrations.

HEI welcomes research proposals to evaluate complex regulatory programs implemented over medium- to long-term time periods. Due to the longer time periods covered, some studies are expected to be retrospective in nature, in which case researchers need to demonstrate that they have access to high quality air pollution and health data (or plan to collaborate with researchers who have such access as shown in a letter of support), as well as data on possible confounding factors occurring over the same time frame. To evaluate upcoming air quality actions, researchers are advised to design a staged approach to ensure collection of appropriate data before the regulatory action is implemented.

1b. Air Quality Actions at the Local (Urban) Scale

Recently, many cities have started to implement actions to improve air quality. Early efforts to address traffic congestion were implemented in e.g. London, Stockholm, and Singapore that were hoped to both ease congestion and provide air quality benefits (Ogilvie et al 2006; Tonne et al 2008; Kelly et al 2011a; Broström and McKelvey 2018). Low emission zones (Kelly et al 2011b; Qadir et al. 2013; Fensterer et al. 2014; Morfeld et al 2014; Wood et al. 2015; Mudway et al 2018) encourage more rapid fleet turnover to cleaner technology vehicles by charging older, more polluting vehicles for entering the city center. Other cities have limited driving days for cars with certain license plate numbers to reduce the number vehicles on the road on a given day (e.g. Beijing, Mexico City) or have implemented road closures or restricted access of certain streets (e.g. Oxford Street in London). More recently, cities have started to move towards outright bans of certain vehicles, for example diesel vehicles, mainly in Europe.

These actions go hand in hand with efforts to transform urban mobility by, for example, promoting public transportation and active modes of transportation and other alternatives, such as shared driving and bike programs, increasing bike lanes, ‘complete street’ programs and other urban design measures, providing incentives for cleaner technologies (e.g., use of the cleanest diesel vehicles, conversion to electric, hydrogen, or natural gas), and early efforts to plan for and encourage new disruptive technologies (e.g. autonomous vehicles). 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. HEI welcomes research proposals to evaluate the effectiveness of such city-level measures (both in large and smaller cities) to improve air quality and public health and encourages researchers to work with local communities where appropriate. Such city-level measures will need to be in active implementation – and large enough to have potential measurable effects, rather than solely being in the planning stage.

Large, highly populated cities could also be useful locations to evaluate national or regional regulations targeting specific sources or changes in vehicle technologies such as clean diesel. Some European cities are planning to ban fossil fuel vehicles altogether, promoting electrification of urban transport. Each of these actions potentially reduces neighborhood concentrations of traffic-related air pollution and thereby potentially affects health outcomes. Applicants should bear in mind that early studies to evaluate the effectiveness of such actions have been challenged by relatively small changes in air quality and limited study power due to the potentially small area covered.

HEI welcomes proposals to evaluate shorter-term, local interventions to improve air quality and health. Proposals should provide information on study power to ensure changes in air quality and health can be detected, and particularly pay attention to selection of control areas or populations as well as meteorology and background concentrations of various pollutants, as discussed elsewhere.

1c. Regulatory Actions Targeted at Major Ports and Transportation Corridors

HEI is inviting proposals to evaluate the effectiveness of complex programs leading to reduced emissions in the vicinity of major ports and transportation corridors and aimed at improving public health of populations affected by such emissions. Studying such complex actions requires understanding of the sets of rules being implemented and their timeline of implementation, estimation of the emissions reductions over multiple years, as well as actual, high-quality monitoring data over the study period.

Over the past decade, California, New York, and other states have implemented or begun to implement programs aimed at reducing emissions from "goods movement" (California Air Resources Board 2006; Su et al 2016). Major marine ports are serviced by marine vessels, harbor craft, railway locomotives, heavy-duty trucks, and cargo handling equipment and are large contributors to concentrations of particulate matter and nitrogen oxides, mostly from diesel engines. In addition, ports are often situated in, or close to, densely populated areas, with a relatively high percentage of disadvantaged populations (National Environmental Justice Advisory Council 2009). Air quality management programs in ports have to target multiple sources in order to be effective: measures may include providing shore power for ocean-going vessels while docked in the harbor, reducing sulfur concentrations in marine fuel, reducing maximum speed when ships approach or leave the harbor, and targeting emissions from heavy-duty trucks, locomotives, and non-road equipment through requirements for aftertreatment on new diesel engines and retro-fitting of older engines (see e.g. California Air Resources Board 2006). 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 aimed at improving air quality for people living in ports and coastal communities.

Similar issues regarding air quality, freight movement by trucks coming and going, and disadvantaged communities being located nearby apply to airports. Specific issues surrounding airports that have been studied are exposure to ultrafine particle emission from airplanes and noise issues (Hudda et al. 2014; Masiol and Harrison 2014; Huang et al 2015; Keuken et al. 2015; Shirmohammadi et al. 2016; Benosaa et al 2018). Currently, there is a paucity of studies evaluating the mitigation of emissions and noise sources and the effectiveness of such measures. Thus, HEI is interested in studies to evaluate the effectiveness of such regulations and actions in improving air quality and health in the vicinity of both marine harbors and airports.

HEI welcomes research proposals to evaluate changes in health outcomes of coordinated, complex emissions reductions programs targeted at specific transportation corridors or hubs, as well as proposals to specifically evaluate health outcomes of reducing emissions in marine harbors and airports.

2. Develop and Apply Methods to Conduct Accountability Research

RFA 18-1 also seeks proposals for methods development, either as part of a study of specific actions taken to improve air quality or as a standalone project to develop the needed statistical and epidemiologic tools or to test proposed methods in a specific population or database (e.g., a large cohort or a previously studied, dynamic population). Examples of currently needed methods development and refinement include the following:

More robust research designs and statistical methods better suited to estimating the health effects of air quality interventions are clearly needed. Improvements in epidemiologic and statistical methods in air pollution epidemiology, and environmental epidemiology more generally, over the past decades have led to advances in knowledge and methodology (Thomas 2009). The application of Bayesian hierarchical models and spatial statistics and of other geographic methods has led to better estimates of the risks of adverse health outcomes associated with long-term exposure to air pollution (Zeger et al. 2008; Krewski et al. 2009; Zigler and Dominici 2014a). Accountability research is challenging in part because it must account for both temporal and spatial patterns in the data, as well as confounding and mediating factors (HEI Accountability Working Group 2003; van Erp and Cohen 2009). This added complexity may well require new approaches, such as: 1) methods for mediation analysis (VanderWeele 2016) and / or principal stratification for disentangling different pathways of how an air quality action might affect health (e.g. through desired reductions on air pollution levels or through alternative pathways) (Zigler et al 2012, 2018); 2) including computationally intensive methods from other disciplines not currently employed in air pollution epidemiology.

Because the effect on health of further reductions in air pollution are likely to be small, particularly in high income countries, it is important to develop a reasonably 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. Many studies will, of necessity, be retrospective, and the size of the study population will be fixed. Therefore, it will be critical to pay serious attention to the sensitivity of statistical inference to model specification and time-varying confounding (e.g. Robins et al 2000; Zigler et al 2016; Zigler and Dominici 2014b) or implement quantitative bias analyses (Lash et al 2014; Weave et al 2018).

CRITICAL STUDY DESIGN CONSIDERATIONS

HEI Communication 14 (van Erp and Cohen 2009) and Communication 15 (Health Effects Institute 2010) identify in detail a range of important design considerations for all accountability research. A number of these considerations are summarized below. The ability of any proposed study in response to this RFA to address and integrate these considerations will be a central factor in decisions on funding.

Pre-intervention baseline. Studies of planned actions to improve future air quality (a prospective study design) and studies of actions taken in the past (a retrospective study design) will both be considered. In either case, investigators will need to be able to document baseline (i.e., pre-intervention) air quality and health conditions. Prospective studies are potentially the most informative but will usually require that investigators identify proposed actions in advance and begin work early enough to provide stable estimates of baseline conditions. It may be useful to establish links with local authorities and communities at an early stage. Proposals that already have available or can acquire good baseline data will be at an advantage. Applicants may consider using scenario approaches that compare conditions after an intervention with predicted conditions under a "counterfactual" scenario without the intervention (see e.g. Russell et al 2018).

Duration. The duration of studies funded under the RFA is generally limited to three years, with the exception of prospective studies of long-term air quality actions that can be extended to 4 years with proper justification or should be designed in stages that can be funded separately to capture both baseline conditions and changes after implementation of the proposed regulation. If this is the case, the proposal should identify a clear set of deliverables for each stage.

Concurrent environmental changes and potential confounding. The need to account for background trends in air quality and health will be both critical and challenging. Other environmental, economic or other factors changing in the same time-period as the air quality intervention could affect exposure to air pollution as well as public health and thereby may confound the estimation of effects of the regulation or other intervention.

Generally, researchers should approach this question as "What conditions *other than the intervention* could explain the observed changes in air quality or health and how can we account for their influence on the outcome?" To this end, it is recommended to include appropriate comparison or control populations that are unaffected, where possible; it is also recommended to conduct detailed simulation and sensitivity analyses to evaluate choices of reference populations and of statistical models adjusting for background trends and other factors.

Mediation. Regulatory interventions to improve air quality may result in changes of behavior within target populations that may in turn affect health. Researchers are encouraged to specify and investigate the potential different pathways through which the air quality action acted upon health.

Time period of interest. This requires consideration of 1) the time lag between the propagation of an air quality action and the time at which an effect of the action on air quality and health can be expected to occur;

2) temporal trends in population structure (e.g., demography) that may alter the susceptibility of the population to various adverse health outcomes; 3) changes in medical access as well as public health practices that lead to improved outcomes for particular diseases; 4) changes in the distribution of health-related behaviors — for example smoking — within and among populations; 5) effects of regulatory changes for a given pollutant on the overall mixtures to which populations are exposed; and 6) the often heterogeneous patterns of change in pollutant levels due to a regulatory action across time and space. Knowledge of implementation, enforcement, and compliance of the air quality action is crucial in understanding the time frame over which air quality changes are expected to occur.

Exposure estimation. Considering general trends in regulations and air pollution research, studies should include multiple air pollutants, with particular focus on $PM_{2.5}$,NO_2 / NOx and O_3. Even if proposed studies focus on pollution mixtures, information about the contribution of individual pollutants to potential health benefits will be very valuable. Studies should develop and evaluate exposure assessment methods suitable to estimate changes in exposure related to the air quality action at relevant spatial and temporal scales. Studies may rely on data from existing ground-based monitoring networks or satellite data and/or previous and/or future measurement campaigns to collect monitoring data; most existing monitoring networks have insufficient density to capture small-scale variation of air pollution, particularly relevant for an evaluation of local interventions. If measurement campaigns are proposed, studies should preferably use standardized and routine sampling methods. However, some studies may offer the opportunity of including new instruments, low-cost sensors, or wearable devices. If such approaches are proposed, applicants should provide a rationale for their inclusion, evidence regarding the performance and quality of the data, and a detailed QA/QC plan for use of the instrumentation; cross-validation with existing ground-based monitoring under various conditions would be useful. Studies using satellite data should also discuss the appropriateness of the data for the desired spatial scale.

Outcomes of interest. This RFA does not target specific health outcomes. However, applicants should give a clear rationale regarding the choice of health outcomes in relation to the research questions being addressed and the relevance of such questions for policy. Preference will be given to health outcomes that are well-justified and for which evidence of a link with air pollution has been reasonably well-established recently in authoritative reviews such as the U.S. EPA's 2016 NO_2 and 2009 PM Integrated Science Assessments (Environmental Protection Agency 2009, 2016), the World Health Organization (WHO 2013, 2016), and the Committee on the Medical Effects of Air Pollution (2016, 2018a, 2018b).

Precision and statistical power. Proposals should present detailed estimates of the predicted air quality changes of the regulatory action and show sufficient power to detect health effects, i.e. a large enough air quality improvement to expect a detectable change in health status that can be attributed to the intervention. To this end, applicants should conduct a formal power calculation, and conduct simulations, where appropriate, to inform study design. Applicants should discuss the expected precision and statistical power in detail.

Statistical methods Applicants should propose appropriate statistical and analytical methods. Because model selection can have an impact on the outcome, sensitivity analyses of the key modeling choices should be included. To address the objectives of the RFA improved statistical approaches may be developed (see also #2 *Develop and Apply Methods to Conduct Accountability Research*). HEI requires applicants to include sufficient statistical expertise on the study team and strongly recommends their involvement during study design and preparation of the application.

Dissemination of methods and results. HEI expects researchers to develop plans for access to data and methods. Any methods developed under this RFA should be useful to other researchers with training in epidemiology and statistics. Please consult HEI's **data access policy** (www.healtheffects.org/accountability/data-access-transparency) for details.

WHO SHOULD APPLY?

HEI welcomes applications from academic and other public and private research institutions in the US, Europe, and elsewhere. Successful research proposals will in most cases require the collaboration of experts in air pollution measurement and assessment of human exposure, epidemiology, medicine, risk assessment, and biostatistics. Our experience in evaluating the previous rounds of accountability research proposals confirms the importance of the active involvement of each key discipline in the study design. Any poorly developed component may affect the disposition of the entire proposal. Researchers are encouraged to consult government and policy experts to find out about opportunities to study specific regulations and obtain a good understanding of their scope and implementation schedules.

Role of Government Agencies and Private Industry

Active cooperation of government regulatory and public health agencies may also be necessary for this research, but as would be the case with any research that HEI might fund, we cannot consider applications from employees of environmental regulatory agencies at the local, state, or federal levels who are responsible for developing and implementing regulations or from employees of private industries who are responsible for complying with such regulations. Such individuals may, of course, play roles as purveyors of data or other information that they collect and maintain and may be compensated by the investigators for reasonable costs entailed in providing such information. Employees of governmental agencies (such as state and local departments of public health) who do not usually have responsibility for promulgating or implementing actions to improve air quality may apply for and receive funding to conduct research under RFA 18-1.

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