Particulate Matter Research Centers

The U.S. Environmental Protection Agency (EPA) announces an extramural funding competition for Particulate Matter (PM) Research Centers to address priority research needs related to airborne PM, including susceptibility, mechanisms of health effects, exposure–response relationships, and source linkages. This announcement provides relevant background information, summarizes the EPA's interest in supporting these centers, and describes eligibility requirements and application instructions for the program. Information regarding current research can be found on the Office of Research and Development's National Center for Environmental Research (NCER) homepage at http://es.epa.gov/ncer/science/pm.

In appropriating fiscal year 1998 funds, Congress urged the EPA to establish as many as five university-based research centers focused on PM research. The EPA issued a competitive request for applications (RFA) in 1998, and awarded five-year grants to five PM research centers in 1999. These centers are now completing their fifth year of work. This RFA is a new competition for PM Research Centers. It is open to both new center applicants and existing PM Research Centers. All applications will be evaluated by an external peer review panel convened by the NCER's Peer Review Division. Subsequently, the most highly rated applications will be considered by EPA scientists and managers in order to select the next set of centers that will best address the key research issues identified in this solicitation.

This RFA includes a description of the research needs that the PM Research Center applicants will address. These needs are broad, reflecting a cross-cutting theme of linking health effects with PM from source categories and components. The EPA recognizes that not every applicant will address all of the topics specified in this RFA. However, the most critical science questions faced by the agency's PM research program are multidisciplinary in nature.

The most successful applicants will take an integrated approach that addresses in a scientifically sound manner aspects within the continuum of PM sources to effects. Applicants are required to demonstrate how the various projects contained within their proposals are fully integrated, encourage participation of investigators with the most appropriate expertise, and employ cutting-edge approaches.

In contrast with individual grant awards that focus on a specific research question, PM Research Centers present the opportunity for investigators from different disciplines to work together on larger problems than could be addressed in a single grant proposal. An example of such integration might include atmospheric scientists and health scientists working together to better understand the kinds of PM emitted from a source category, changes in PM composition over time or geographical distance, and the health effects associated with exposure to different PM types.

Applicants should focus proposals on the science questions in which the applicant has demonstrated expertise rather than extending beyond core strengths simply to address many topics. Proposed centers may include arrangements that bring together institutions with strengths in different disciplines, provided they can demonstrate how effective integration in planning and implementing research will be achieved.

Centers may be funded for up to five years; applications should clearly show how the program might evolve during that time. A successful application will recognize that PM research priorities must evolve as new data are generated, and will include a detailed description of the process by which the center will set priorities and phase in new activities, as appropriate. An iterative process might be used, for example, in which interpretation of new results in health studies will influence subsequent studies in exposure and source apportionment, the results of which may influence further health studies. The process should lead to a better understanding of the source–concentration–exposure–dose–response continuum.

The National Research Council (NRC) has published four reports that recommend and discuss a portfolio of research activities targeted to address the highest-priority PM research needs. Since the expanded investment in PM science by Congress in 1998, progress has been made in many areas of PM research by the EPA's intramural research laboratories, through the EPA's grants and centers programs, and through other research programs. To identify the areas of focus for this RFA, the EPA has evaluated the NRC research priorities, the Committee on Environment and Natural Resources Air Quality Research Subcommittee PM research strategy, the NARSTO PM Assessment, and the EPA Science Advisory Board's interim review of the PM Research Centers, and has considered the research activities currently under way. This RFA emphasizes priority research areas needed to promote scientific understanding of the linkages between sources, PM components and physicochemical attributes, exposure, and health effects. Through this RFA, the EPA is soliciting proposals to develop research centers that construct well-defined and integrated programs addressing PM research needs in the areas of susceptibility, mechanisms of health effects, exposure–response relationships, and source linkages.

In its 1998 report, and reiterated in 2004, the NRC PM committee described a source-to-response framework. This framework continues to provide a useful structure for identifying and organizing PM research priorities. This RFA relies on the source-to-response continuum as a cross-cutting theme to facilitate the integration of PM research proposals.

EPA research continues to address the health effects of PM characteristics and constituents, but increasingly, key research questions are focusing on linking these PM attributes to source categories. Research is needed to understand relationships between PM components/attributes emitted from emission sources and the resulting ambient concentrations and human exposures. Research is also needed to understand the relative toxicity of different PM components/attributes, and to link these back to emission sources and exposures. Collectively, this information can help identify those sources and attributes of PM contributing to the most hazardous exposures.

As emphasized by the NRC PM committee in its final report, some progress has been made in identifying specific attributes or chemical components of PM, but there are still critical gaps in our understanding of the contribution of PM components (e.g., organic compounds) and attributes (e.g., different size fractions of PM) to the observed health effects associated with PM. Studies are encouraged that lead to a better understanding of health effects caused by different physical characteristics of particulate matter (e.g., coarse, fine, and ultrafine size fractions) or by aspects of the physical chemistry of PM. Also of interest are studies that link health effects with variations in exposure or response related to PM components, such as organic carbon, elemental carbon, and inorganic components such as sulfates, nitrates, and metals. Additionally, studies are encouraged that address PM alone or in combination with copollutants such as ozone, nitrogen, and sulfur oxides. Of particular interest are studies that determine if these interactions are additive or synergistic in nature, as well as characterize the resulting adverse health effects and underlying mechanisms of such interactions.

Described below for each priority research area is a brief overview of the research needs that the PM Research Centers are anticipated to address. The proposed projects and integrated application should indicate how the research will contribute to improved understanding of key elements of the continuum from sources through PM components/attributes to health effects.

Susceptibility to PM effects. Increasing our understanding of who is susceptible to the effects of PM, and why they are susceptible, will improve the scientific basis for air quality standards and will aid in the development of strategies for minimizing the effects of PM on these susceptible groups. With the understanding that PM can act systemically, rather than impacting only the lungs, emerging evidence suggests there may be specific susceptible populations other than those already identified. Additionally, certain windows of vulnerability (e.g., during fetal development, during a viral infection) may increase susceptibility. Some studies have suggested that other factors such as socioeconomic status, race, or gender may play a role in susceptibility to PM-related effects, but only limited and inconsistent evidence on such groups is available. In addition, long-term exposure to PM may move an individual into a susceptible "pool" where acute exposures to multiple stimuli (e.g., tobacco smoke, pathogens, paint fumes, other air pollutants) could cumulatively induce adverse health effects. Furthermore, different components or other PM attributes may target people with different susceptibilities (e.g., people with asthma may be especially susceptible to biologic components present in PM).

To address the questions of susceptibility, proposals may employ any number of approaches including *in vitro*, animal, controlled human exposure, panel studies, small clinical studies, and epidemiological studies. This RFA encourages novel application of appropriate animal models, including naturally susceptible, disease-induced, and genetically or pharmacologically manipulated models. The innovative use of *in vitro* models is also encouraged.

Specific issues of interest include 1) What previously unrecognized subpopulations are susceptible to PM-induced health effects? 2) What are the personal factors (e.g., disease state, diet, genetics, socioeconomic status) that influence susceptibility to effects of PM? Are these personal factors different for acute versus chronic exposure to PM? 3) How do these factors contribute to making "healthy" people permanently or temporarily susceptible to the adverse effects from exposure to PM? 4) What underlying biological mechanisms are responsible for effects in susceptible populations? (see "Biological mechanisms for PM effects" topic below.) 5) Do certain subpopulations have unique PM component exposures by virtue of personal factors? If so, what is their impact?

Biological mechanisms for PM effects. The mechanisms by which PM, or other air pollutants, cause adverse health effects are not yet adequately understood. PM consists of many different components and size fractions, all of which may tender health outcomes by different mechanisms. In addition, PM affects different organ systems and is likely to cause adverse effects in these systems by different mechanisms. Finally, it is likely that the underlying mechanisms are different for acute and chronic effects.

For the purpose of this RFA, mechanistic research refers to hypothesis-driven studies that seek to define the molecular, biochemical, cellular, or physiological mechanisms that underlie a biological change induced by exposure to PM. For example, studies that describe changes in heart rate variability or pulmonary inflammation induced by PM exposure would not be considered mechanistic. However, studies that characterize the underlying processes responsible for changes in heart rate variability or pulmonary inflammation would be considered mechanistic.

This RFA promotes novel application of appropriate animal models, including naturally susceptible, disease-induced, and genetically or pharmacologically manipulated models. The innovative use of *in vitro* models is also encouraged. The use of state-of-the-art molecular biology, genetic, genomic, proteomic, and metabolic profiling techniques to address these questions is equally encouraged.

Examples of specific areas of interest include 1) What are the physiological, cellular, biochemical, and molecular mechanisms by which PM causes acute and/or chronic adverse health effects? 2) Do different PM components, or PM derived from various sources, cause adverse health effects by different mechanisms? How do the mechanisms differ? 3) How do the mechanisms that underlie health effects following exposure to high concentrations of PM differ from mechanisms responsible for effects following exposure to low concentrations of PM? 4) How are the mechanisms that underlie the response of susceptible animals or humans different from those that occur in healthy individuals?

Exposure–response relationships. Epidemiological studies have established that exposure to ambient PM is associated with adverse health effects, but much remains to be learned about the nature of PM exposure–response relationships. In understanding PM exposures, researchers have made progress in identifying correlations between central site measurements of ambient PM mass and personal exposure to total, ambient, and nonambient PM, and information is emerging on the key factors that affect these correlations. However, it is not clear whether these correlations are also true for individual PM components or attributes. Better understanding of personal PM exposures is needed to improve exposure assessment models used in epidemiological studies of PM effects.

Questions remain about how differences in duration of PM exposure affect its impact. For example, short-term spikes of high duration (a few hours) may cause more adverse health effects than longer exposures to lower PM concentrations, even though the amount of PM deposited during a 24-hour period may be similar. Additionally, much of the PM health research to date has focused on effects reported in daily time series studies or in animals or humans acutely exposed to PM. Research on health effects associated with long-term exposure to PM is more limited. The EPA is currently funding several large epidemiological studies examining the effects of long-term exposure to PM and therefore is not seeking additional studies of this type. However, smaller-scale epidemiological analyses that offer new insights may be of interest. Similarly, toxicology studies that characterize the effects of long-term exposure in animals are appropriate, especially if they can lead to a better understanding of susceptibility and mechanisms.

Research is also needed to establish the relationships between personal exposure, dose, and response for a range of exposure conditions. Better information is needed on issues such as high-dose to low-dose extrapolations, and dose–response curves that enable estimations of the proportion of the population expected to experience adverse health effects, depending on their exposure pattern, ventilation, and susceptibility.

For research that addresses questions related to exposure–response relationships, proposals may include a wide range of study approaches, including exposure modeling, animal toxicology, small clinical or panel studies, and epidemiological studies. Approaches that develop improved exposure assessment for panel or epidemiological studies are encouraged.

Specific areas of interest include 1) What are the relationships between ambient concentrations of PM and its attributes, constituents, and copollutants, and personal exposures to ambient and nonambient PM and copollutants? How do human activities, population demographics, housing characteristics, and/or local sources affect personal exposure to ambient PM? 2) How are responses to PM affected by duration of exposure (e.g., short-term peak exposures versus 24-hour exposures) or spatial/temporal variability in PM concentrations? 3) What are the effects of long-term exposure (over weeks, months, years) to PM? 4) What is the shape of the exposure–response function for PM across a concentration gradient that includes ambient exposure levels? How does it vary for different health end points and for PM and its constituents/attributes derived from various sources?

Source linkages. Evidence from numerous toxicology studies has indicated that the type and strength of adverse health effects due to exposure to ambient PM vary as the attributes of the PM itself change. The attributes that have been studied in the most detail are particle size and composition, both of which often vary with particle source, and often with the atmospheric conditions through which particles are transported and transformed. Understanding the generation of particles, how these attributes may be changed (or formed from precursor gases) between the point of emission and the point of exposure, and the relative contributions of sources to the ambient PM concentrations in different regions of the country is important for understanding the links between emissions and local air quality, as well as the links between sources and adverse health effects associated with exposure to PM.

Not only do particle attributes vary with source type, but impacts on composition and size result from changes in design or operation of sources within a source type. For instance, changes in engine design over the past decade have resulted in diesel engines that have very different emissions characteristics (including particle attributes) compared to earlier engine designs. In addition, the mode of operation also impacts the size and composition of particles, whether from open vegetative burning, mobile source engines, or stationary utility and industrial sources. To better understand the links from source through atmospheric transformation and exposure to dose and effects, it is necessary to tie the key particle attributes (including, but not limited to, size distribution, organic species, metal content, and bioavailability of particle species) to specific source types, including across different designs and operating conditions.

In addition to understanding the attributes of particles associated with specific sources, it is also necessary to better understand the contribution of source categories to the mix of particles in the ambient atmosphere and ultimately to the particles to which people are exposed. Whereas previous source apportionment efforts have largely focused on source categories that contribute the most PM mass, the importance of some smaller mass sources may increase when considering health effects.

Studies of the health effects caused by ambient particles are of higher value when the sources of those samples can be estimated using methods such as source apportionment. These often require a more thorough understanding of the composition of ambient, personal, and source samples, including concentrations of specific species within those samples. Proposals are encouraged that improve our understanding of the processes that link sources and receptors in such a way that the impact of specific source types or particle attributes on health effects may be more completely understood.

Specific issues of interest include 1) How do changes in source design or operation impact the attributes of emitted, and ultimately ambient, PM? 2) How can the relationships among emission sources, atmospheric concentrations, and personal exposures to ambient PM be understood and represented in different methods and models? 3) How do atmospheric processes in different regions of the United States influence ambient concentrations and the source–receptor relationships that impact observed air quality levels and health effects? 4) How can we apply methods that link sources and receptors to better understand the contribution of source types, components, and attributes to air quality levels and health effects? 5) How can health responses to ambient PM exposure be linked to specific emission sources and/or source categories?

It is anticipated that a total of up to $40 million will be awarded, depending on the availability of funds. The EPA anticipates funding up to five grants under this RFA. The projected award per grant is $1.3–1.6 million per year total costs, for up to five years. Requests for amounts in excess of a total of $8 million, including direct and indirect costs, will not be considered. The total project period for an application submitted in response to this RFA may not exceed five years. Funding in subsequent years will be contingent upon satisfactory progress.

Applications must be prepared using the STAR application found on the Internet at http://es.epa.gov/ncer/rfa/forms/. Additional application requirements as well as the entire text of this announcement can be found online at http://es.epa.gov/ncer/rfa/2004/2004_pm_research.html. Applications must be received by 31 August 2004. The earliest anticipated start date is 1 July 2005.

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