



Interim Review of the Particulate Matter (PM) Research Centers of the USEPA: An EPA Science Advisory Board Report

**A REVIEW BY THE PM
RESEARCH CENTERS
INTERIM REVIEW PANEL OF
THE EXECUTIVE COMMITTEE
OF THE US EPA SCIENCE
ADVISORY BOARD (SAB)**



**UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460**

May 24, 2002

**OFFICE OF THE ADMINISTRATOR
SCIENCE ADVISORY BOARD**

EPA-SAB-EC-02-008

Honorable Christine Todd Whitman
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Subject: Interim Review of the Particulate Matter (PM) Research Centers: An SAB
Report

Dear Governor Whitman:

On February 11 and 12, 2002 the PM Centers Interim Review Panel (Panel) of the US EPA Science Advisory Board (SAB) met to review the Agency's PM Research Centers program as a mechanism for generating research results that can inform Agency decision-making. The request to provide this advice was received from the National Center for Environmental Research (NCER) in the Office of Research and Development (ORD).

In 1998 the NCER, under its Science to Achieve Results (STAR) Program, issued a competitive request for applications that resulted in the support of five PM Research Centers for up to five years, with a total of \$8M expended in the first year of the program. The Centers were to address research needs in the areas of exposure, dosimetry, extrapolation modeling, toxicology, and epidemiology.

As it considers budget formation for FY04 and beyond, NCER needs to decide whether or not to continue with the concept of PM Research Centers beyond the current funding cycle, or whether there might be a better way of generating the research results that will inform Agency decision-making on PM issues. Insufficient time has passed for the Centers – individually or collectively – to have generated a body of research results that could allow a definitive answer to this question based on “outputs”, *per se*. However, considerable experience has been gained with the Centers concept to date that can allow an assessment of the overall utility of this approach, if not of the individual Centers themselves.

This emphasis on the assessment of the concept of Centers-based research is reflected in the Charge to the Panel that consists of an overall question, plus six specific questions:

Overall Question:

Is it likely that the PM Centers program will be sufficiently successful to merit continuation in FY 2004 and beyond? In which areas, to what extent, and for what reasons is a PM Centers program beneficial? Where it is not, what improvements can be made?

Specific Questions:

1. Recognizing the PM Centers program is barely at its halfway point, what important research findings (or promising investigations) have been made that would not have occurred otherwise? What unique aspect(s) of a Centers program enabled such actions to be taken.
2. To what extent has the direction or focus of research shifted as a result of the multi-disciplinary interactions within the Center (i.e., findings in one department influence researchers in another to change direction or emphasis). To what extent have changes in research direction or emphasis been influenced by Science Advisory Committee reviews, interactions with other PM Centers, or interactions with the broader PM research community? Which factors have been most influential?
3. How successful are Centers in communicating their findings to the public and specifically, to those who directly use their research? Is it clear that the work has been supported by the PM Centers program?
4. How, if at all, does a PM research centers program facilitate agreement or consensus on protocols or procedures to enable more direct comparison of results among research institutions or centers?
5. How, if at all, does a PM research centers program leverage or maximize use of resources through sharing expensive equipment, samples, data, etc.?
6. How is the program perceived within and outside the research community? Does a research center have greater visibility, and if so, what is the impact?

Detailed answers to these questions are found in the body of the report. The thrust of the answers are captured in the following major findings and recommendations:

1. The PM Centers Program a) has produced benefits beyond those normally found in individual investigator-initiated grants and b) is likely to continue to provide such benefits throughout its current funding cycle. Overall, the Panel found that the program merits continuation beyond FY04 -- through a new, fully-competitive round of applications -- as one part of a diverse PM research portfolio at the Agency.
2. The Panel identified several specific advantages that the Centers approach offers over more traditional research mechanisms, including enhanced flexibility and adaptability leading to improved timeliness, ability to conduct higher-risk pilot and validation efforts, study designs enhanced by intra-Center multi-disciplinary integration, and improved leveraging of the Agency's and the Centers' research resources.

3. The Panel identified several ways in which a new round of Center grants could be enhanced, either by expanding upon activities already underway or by undertaking new efforts. Importantly, the Panel noted that while there are evident benefits of integration within and across Centers, there are also potential challenges to insure that the work of the Centers does not become isolated from that of other researchers within the Agency and in the academic community. Key enhancements include the following:
- a. Continued attention in a new request for applications (RFA) to focusing the Centers' efforts on the most critical PM needs, as determined at that time in reviews of research progress and needs by the National Research Council and US EPA
 - b. The development of an informal, but overarching, mechanism of scientific advice to the program
 - c. Enhanced opportunities for cross-fertilization of ideas with EPA's intramural researchers and the broader extramural community
 - d. Enhanced interaction between the research conducted at the Centers and ongoing intensive air quality monitoring efforts, such as those at the Agency's supersites and others
 - e. The provision of systems and resources from the start for inter-Center integration efforts.

We appreciate the opportunity to review and provide advice on the PM Research Centers program. We want to acknowledge the valuable assistance of the Agency staff who supplied us with information that is a part of the public record of our meeting. The documentation, presentations and availability of the Center Directors to answer questions during our public meeting were also very helpful.

We look forward to your response to this report.

Sincerely,

/ Signed /

Dr. William H. Glaze, Chair
EPA Science Advisory Board

/ Signed /

Mr. Daniel Greenbaum, Chair
PM Research Centers Interim Review Panel
EPA Science Advisory Board

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EPA Science Advisory Board
Executive Committee
Particulate Matters Interim Review Panel***

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a. SAB Members: Experts appointed by the Administrator to serve on one of the SAB Standing Committees.

b. SAB Consultants: Experts appointed by the SAB Staff Director to a one-year term to serve on ad hoc Panels formed to address a particular issue.

** Dr. Hopke participated in the public meeting of the Panel and contributed material to an early draft of this report. Subsequently, he became associated with the Rochester PM Research Center and resigned from the Panel. Dr. Hopke did not participate in the final deliberations of the Panel and is not a party to the Panel's final report.

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1. INTRODUCTION

1.1 Background

As one of its first and most important environmental legislative actions, the U.S. Congress passed the Clean Air Act (CAA) that authorizes the US Environmental Protection Agency (Agency) to conduct research, assess findings, and develop and implement regulations to control pollutants in the air that adversely impact human health and the environment. For the past thirty years the Agency has used this authority [modified by the Clean Air Act Amendments (CAAA) of 1990], in part, to establish a vigorous National Ambient Air Quality Standards (NAAQS) program. As a result, the Agency has implemented a costly, but effective, regulatory program to reduce the negative impacts of a series of air pollutants.

One of the key air pollutants is "particulate matter" (PM), airborne microscopic particles of whatever composition and shape.

From the earliest days of the Agency, public support was high for the control of "dirty air"; i.e., black, sooty emissions from power plants, industrial facilities, and trucks and automobiles. This support was soon translated into regulations to monitor air concentrations and implement control of emissions that contributed to Total Suspended Particulate (TSP) matter, without a specific size classification. This standard was changed in the late 1980s to include a size criterion that included particles with mass median diameters (MMD) of 10 microns or less (PM₁₀), in recognition of the inhalability of such particles, as compared to those larger than 10 microns. Subsequent research revealed that exposures to PM at the so-called PM₁₀ standard posed unacceptable risks to human populations. As more research results became available, pressure mounted to apply additional monitoring requirements and controls on emissions of smaller-sized PM; specifically, in the MMD 2.5 micron range, on the basis that particles of this size are more likely to penetrate to the respiratory regions of the lung and remain there for longer periods of time. The Agency and the country are currently in the process of implementing these new PM_{2.5} regulations.

Scientific research is playing a large role in monitoring and characterizing PM_{2.5}, establishing its effects on exposed populations, and developing effective control measures to reduce its concentrations in the atmosphere. Prestigious panels of experts have convened under the auspices of such groups as the National Academy of Sciences (NAS), the Agency's Science Advisory Board (SAB), and the Health Effects Institute (HEI). From these panels' deliberations and reports of the NAS Committee on Research Priorities for Airborne Particulate Matter a strategic research plan has emerged that will illuminate the path that leads to making the difficult risk management decisions about regulating the sources of PM_{2.5}.

As a part of the effort to carry out this PM research plan, the Agency issued a request for applications (RFA) in 1999 to establish five PM Research Centers, to be funded at a level of \$8M in the first year of the Centers program. Each Center was to bring multi-disciplinary

expertise to bear on important research questions identified in the RFA as of highest priority. As a result of the competition that drew roughly 20 applications, the following PM Research Centers were established:

- a. Harvard University PM Center - Ambient Particle Health Effects: Exposure, Susceptibility, and Mechanisms
- b. New York University PM Center - Health Risks of PM Components
- c. Northwest PM Center - Combustion-derived fine particulate composition, exposures, and health effects
- d. Rochester PM Center - Ultrafine Particles: Characterization, Health Effects, and Pathophysiological Mechanisms
- e. Southern California PM Center - Sources, Exposure, and Health Effects of Particulate Matter

Roughly half of the five-year grant period for these Centers has passed, and the Agency must soon make a policy decision on whether or not to continue the Centers program, possibly through a second round of RFAs. The Agency has asked the SAB for its technical advice that will inform this policy decision.

There are, of course, other alternatives to conducting research via a Centers-based mechanism; e.g., awarding a large number of investigator-initiated grants. In order to evaluate the relative merits of a Centers-based program versus other alternatives, it would be helpful to have the research products from the current mechanism available to compare to the research outputs from those alternatives. In this case, however, after only two and half years, the research results from the Centers are just now beginning to appear in significant number in the scientific literature, so it is too early to assess these outputs definitively *in toto*. At the same time, sufficient experience has been gained from the Centers to date to allow a reasonable estimate of the major strengths, weaknesses, and potential of the Centers-based mechanism as a means for generating the kind of research results than will be needed by the Agency.

1.2 Charge to the Committee

Acknowledging the limitations inherent in this exercise, the SAB convened a group of experts, whose knowledge and experience -- individually and collectively -- qualify them to address the specific set of questions (the Charge) posed by the Agency.

Overall Question:

Is it likely that the PM Centers program will be sufficiently successful to merit continuation in FY 2004 and beyond? In which areas, to what extent, and for what reasons is a PM Centers program beneficial? Where it is not, what improvements can be made?

Specific Questions:

1. Recognizing the PM Centers program is barely at its halfway point, what important research findings (or promising investigations) have been made that would not

have occurred otherwise? What unique aspect(s) of a Centers program enabled such actions to be taken.

2. To what extent has the direction or focus of research shifted as a result of the multi-disciplinary interactions within the Center (i.e., findings in one department influence researchers in another to change direction or emphasis). To what extent have changes in research direction or emphasis been influenced by Science Advisory Committee reviews, interactions with other PM Centers, or interactions with the broader PM research community? Which factors have been most influential?
3. How successful are Centers in communicating their findings to the public and specifically, to those who directly use their research? Is it clear that the work has been supported by the PM Centers program?
4. How, if at all, does a PM research centers program facilitate agreement or consensus on protocols or procedures to enable more direct comparison of results among research institutions or centers?
5. How, if at all, does a PM research centers program leverage or maximize use of resources through sharing expensive equipment, samples, data, etc.?
6. How is the program perceived within and outside the research community? Does a research center have greater visibility, and if so, what is the impact?

1.3 SAB Review Process

The PM Research Centers Interim Review Panel (Panel) was recruited following nominations received from SAB Members and Consultants, the Agency, and the public. The Panel met in public session on February 11-12, 2002 in Room 6013 of the EPA headquarters in the Ariel Rios Building at 1200 Pennsylvania Ave. NW in Washington, DC. Written contributions from the Panelists, prepared before the meeting, modified on the basis of discussions at the meeting, and made available to the public, form the basis for this report. A more detailed description of the SAB process for this review can be found in Appendix B.

1.4 Format of this Report

Following this Introduction, the report provides specific responses to the questions in the Charge to the Committee (Chapter 3). Since a) the basis for the answers the Charge questions are not totally independent and b) the responses to the questions were crafted by subgroups of the Panel for subsequent consideration, editing, and adoption by the full Panel, a given point may be repeated in several contexts throughout the report. However, the transmittal letter and a summary of major findings and recommendations (Chapter 4) seek to focus more succinctly the Panel's thoughts. A series of three appendices (a list of acronyms, a more detailed description of the SAB process, and an abstract) completes the report.

2. RESPONSE TO THE CHARGE

2.1 Overall Question

2.1.1 Is it likely that the PM Centers program will be sufficiently successful to merit continuation beyond 2004?

The PM Centers Program a) has produced benefits beyond those normally found in individual investigator-initiated grants, and b) is likely to continue to provide such benefits throughout its current funding cycle. Overall, we find that the program merits continuation beyond FY04 and suggest below areas in which its efforts can be enhanced.

The Centers have been and promise to continue being an important part of the PM research portfolio of the Agency. At the same time, there are clear advantages to maintaining a diverse research portfolio; e.g., by ensuring that the widest range of investigators are contributing ideas to the PM program and by providing opportunities for cross-fertilization of ideas between the PM Centers and other investigators at the Agency and in the greater research community. Specifically, the Agency should continue to fund the other intramural and extramural components of the overall PM research effort. Within that overall effort, maintaining the PM Centers program in roughly the same proportion to the rest of the PM research program will enable continued benefits to flow from the PM Centers program.

To take full advantage of the benefits and collaborations afforded by a Centers program, continuation of the program should be based on a new, fully competitive RFA process, designed in keeping with the opportunities for enhancements described below. The Centers program should continue to be focused on addressing the PM issues relevant to the policy and regulatory needs of the Agency, including the ability of the Centers to contribute to the replication of key studies. Specific needs to which the Centers would be directed in a new round could include the same topics (i.e., exposure and health) and/or new topics (e.g., source characterization and assessment of emerging technologies). The areas should be defined by the Agency, based on reviews of the priorities and accomplishments to date by the National Research Council (NRC) Committee on Research Priorities for Airborne Particulate Matter and as part of an overall assessment of progress to date and needs that are or are not being met by all elements of the portfolio. The number of Centers to be funded should be developed within a flexible framework and determined based on a) the availability of adequate resources to provide funding, per Center, at a minimum comparable to that provided in current Centers, adjusted for inflation, and b) the availability of high quality proposals which meet the test of intensive peer review.

2.1.2 In which areas, to what extent, and for what reasons is a PM Centers program beneficial?

In its review, the Panel considered a wide range of activities underway at the individual Centers, plus the results of initial efforts at integration across Centers. Drawing on its extensive experience with the alternative to Centers-type grants -- the individual investigator grants -- the

Panel identified several specific advantages that the Centers approach offered over these more traditional mechanisms. These advantages include the following:

- a. Enhanced flexibility and adaptability, leading to improved timeliness.

From the integrated Centers report reviewed by the Panel and presentations made at the meeting, it appears that the time for hypothesis generation and experimental design has been decreased and that hypotheses are being "vetted" through inter-Center communication before laboratory studies have been actually begun. One example of this was the decision following cross-Center collaboration to initiate relatively rapidly a subchronic animal exposure experiment at the NYU center.

- b. Continuity for five years, allowing longer term planning and research implementation.

In contrast to the normal project-specific grant, the Centers appear able to invest in longer-term strategies on important questions; e.g., the systematic efforts by the Washington Center to develop a biomarker for exposure to wood smoke and the detailed follow-up by the Los Angeles Center of new exposure parameters for the Southern California Children's Health Study (CHS).

- c. Ability to pursue higher-risk and more difficult to finance efforts in methods development, validation, and pilot studies, providing a greater potential for innovation.

Efforts at methods development and validation often fare poorly in traditional competitive grant programs, and yet they are essential to advancing the state of the science. Centers offer the ability to undertake these efforts and, then, to field test them. In its review, the Panel identified several such efforts; for example, the extensive inquiry at the Southern California Center into quinones exposures and effects; the development through the Rochester Center of new techniques for using CT scans in dosimetry; the development at the Northwest Center of new particulate carbon personal sampling techniques; and the assessment of source impacts and housing factors (ventilation) on effects estimates of the PM-hospital admissions relationship from the NMMAPS study and the more detailed evaluation of the harvesting phenomenon conducted by the Harvard Center.

- d. Improved study designs, resulting from intra-Center multi-disciplinary integration.

The PM Centers program has allowed for the development of a critical mass in interdisciplinary research at individual Centers. In concept, a Centers grant forces interdisciplinary planning and coordination at the inception of study design, rather than as an afterthought, thereby leveraging the value of interdisciplinary research as a whole. When epidemiologists, exposure experts, aerosol scientists, toxicologists, physiologists, and other scientists engage a problem collectively, there is a higher likelihood of a cohesive, comprehensive approach to the research than when research is assembled from the ensemble of

individually conducted research projects at the same institutions. Just two, among several, successful examples of this interaction at the current PM Centers are

- 1) The integration of toxicology and epidemiology at the Harvard Center to iteratively explore the connection between potential sensitive populations and the cardiac effects of PM exposure.
- 2) The cross-disciplinary work among aerosol scientists, toxicologists, epidemiologists, and exposure assessors to test the effects of mobile source exposure at the Southern California Center.

e. Substantial potential benefits, resulting from inter-Center integration

Although the initial years of the PM Centers have been focused primarily, and understandably, on the development of integrated programs within each Center, there is some evidence of successful efforts to integrate research across Centers, especially following recent efforts by the Agency to foster this collaboration through the development of the integrated reporting for this review. Examples of these emerging benefits include the Rochester workshop on investigation of cardiac effects across disciplines and the development of pooled analyses of childhood effects in the Harvard 24 Cities Study and the Southern California CHS.

f. Demonstrated ability to "leverage" additional resources, resulting in an overall enhancement in research of interest to the Agency

The existing and new studies funded by other organizations and by other Agency programs presents an important benefit to EPA, leveraging its limited funds for PM research and gaining access to the additional science generated on this broader scale. By providing a "critical mass" of experience, interest, and expertise, a Center becomes attractive to outside funding agencies as a credible source for generating answers to their questions in a cost-effective way. Specifically, the breadth of PM health effects research at most of the Centers is significant and appears to exceed substantially the \$1.5 million/year contributed by the Agency's PM Center program. Several Centers provide concrete examples where their programs have allowed them to obtain additional funds; e.g. leveraging between the Northwest Center and the EPA Cooperative Agreement exposure assessment study and the Harvard Center's use of data collected by the Electric Power Research Institute (EPRI)-supported St. Louis bus study.

g. Other benefits, enhancing the value of the Centers Program

In addition to these larger benefits of the PM Centers Program, the Panel identified several other specific benefits that appear to be emerging at different Centers, including the following:

- 1) The ability to adapt and apply technologies/methods developed elsewhere to the work within Center programs; e.g., the application of animal exposure techniques for concentrated ambient particles from Michigan State

University to the design of similar efforts at the Southern California Center.

- 2) The attracting of established researchers in fields other than air pollution to participate in air pollution studies; e.g. experience at the Rochester and the Southern California Centers.
- 3) The thoughtful and carefully planned additional use of existing epidemiology and other data bases for dose-response and other follow-up; e.g., the Harvard Center follow-up of the Six Cities data set and of the NMMAPS morbidity data set for dose-response. It is likely that this process first began at the time that the original Center proposals were prepared. This is a particular benefit of the Center approach, since under a traditional individual grant-based approach, it is unlikely that these additional analyses would have been completed due to the time pressures on investigators who are required to apply continually for additional funding.

In summary, it is clear that there are substantial benefits possible in a Centers Program that complement and expand upon other approaches available to the Agency, both intramurally and extramurally. Given this evidence, the Panel recommends that the program be continued in a new round of Centers-concept funding, so long as adequate resources are maintained to ensure the critical mass necessary to success within each Center. The Panel further suggests that this Centers-based approach may be useful in other aspects of the Agency's program; e.g., the need to develop approaches to study the air pollution mixture, not just its individual components.

2.1.3 What improvements can be made in the Centers Program?

Having concluded that the Centers Program merits continuation, the Panel identified several ways in which a new round of Center grants could be enhanced, either by expanding upon activities already underway or by undertaking new efforts. Importantly, the Panel noted that while there are evident benefits of integration within and across Centers, there are also challenges to insuring that the work of the Centers does not become isolated from that of other researchers within the Agency and in the academic community. Several of the enhancements suggested below aim to ensure this broader cross-fertilization of ideas.

Specifically, the Panel sees the following opportunities for continued benefits and improvement:

- a. A new RFA should seek answers to a clear set of priority research questions, based on current assessments of the state of knowledge, including those from the NRC, and the degree to which other PM investments (Agency intramural, as well as Agency and other extramural) are already meeting those needs. This focused approach was followed quite usefully in the first RFA and should be continued.
- b. There should be systems established and resources available, from the start, for inter-Center collaboration. The Panel noted that the request for an integrated summary report of the Centers -- which was prepared for this review -- both documented

current efforts and had the added benefit of substantially increasing cross-Center communication and the identification of opportunities for integrated activities. Future Centers could be encouraged to engage in this communication earlier, perhaps with an Agency requirement for such reports on a regular basis.

- c. As the PM Centers program matures, there is a need for a mechanism that could provide overarching scientific advice and direction. Although the Panel was hesitant to recommend another layer of formal oversight, it did feel that enhanced advice and direction could be achieved, perhaps through incorporation of a regular meeting of Chairs and/or participation of other “outside” representatives of the Center Science Advisory Committees (SACs) into the annual Directors meeting. This enhancement would
 - 1) Provide opportunities for systematic comparison of results from across Centers and beyond; e.g., exposures and effects of PM from different sources.
 - 2) Enable identification of new opportunities for collaboration among Centers and with the Agency and others in the research community.
- c. To ensure that the Centers do not become isolated from the rest of the scientific community, there is a need for regular opportunities -- perhaps as a public part of the annual Center Directors meetings -- for interaction and cross-fertilization of ideas with:
 - 1) Agency intramural researchers
 - 2) The large number of other PM researchers (STAR grants, other US funding sources, Canada, Europe, etc.)

These activities could result in an additional benefit to EPA by providing a mechanism for keeping abreast of the state of the science on PM issues.
- d. It would be useful to see enhanced interaction between the research conducted at the Centers and ongoing intensive air quality monitoring efforts, such as those at the Agency's supersites and others. (The Southern California Center provides a model of how this might be done. Interaction with NARSTO would provide other opportunities.) The detailed air quality data collected at these sites should be utilized as much as possible by the epidemiology community. In general, it will be important for the various Centers to consider the chemical composition, as well as size, of constituents of PM in their research designs.
- e. There should be expansion and formalization of the current visiting scientists program at some of the Centers in order to take advantage of the Centers as data, methods, equipment, and subject information repositories where scientists could come to focus on specific issues, while utilizing Center expertise and resources.

With these opportunities for enhancement, the PM Centers Program should be able to continue to contribute substantially to the overall Agency PM Research Program.

2.2 Specific Charge Questions

2.2.1 Results to-date

Q 1: Recognizing that the PM Centers program is barely at its halfway point, what important research findings (or promising investigations) have been made that would not have occurred otherwise? What unique aspect(s) of a Centers program enabled such actions to be taken?

Q2: To what extent has the direction or focus of research shifted as a result of the multi-disciplinary interactions within the Center (i.e., findings in one department influence researchers in another to change direction or emphasis). To what extent have changes in research direction or emphasis been influenced by Science Advisory Committee reviews, interactions with other PM Centers, or interactions with the broader PM research community? Which factors have been most influential?

The Panel determined that these two questions were at the core of its charge and, therefore, spent the bulk of its effort having members with particular expertise (e.g., in epidemiology, exposure assessment, monitoring and air chemistry, toxicology, science management, etc.) review the Centers' progress, in depth, from the perspective of that expertise. The results of these expertise-focused reviews are summarized in the subsections that follow below and, in some cases, draw *verbatim* from material presented later in the report. A number of views/themes are repeated in these different reviews and provide the basis for many of the overall conclusions of the Panel generated in response to the overall charge question above (see Section 3.1).

a. Epidemiology

The epidemiology studies in the Centers to date have been partly extensions of ongoing studies, partly more detailed analyses of existing data bases, and partly new field or panel studies, a reasonable approach given that a significant fraction of air pollution epidemiology uses data collected for other purposes. The Centers program allows analysis of a series of specific questions (e.g., on harvesting and threshold/non-threshold issues) that would be difficult to fund using separate grants. Therefore, the Centers program is contributing to efficient utilization of ongoing studies and existing databases. Although it is hard to judge whether these analyses would not have been done without the Centers program, it seems clear that results are now being produced more quickly.

A further advantage of the Centers funding mechanism is the flexibility and discretion that it provides to the Principal Investigator (PI) over a five-year period to direct funds in interesting directions without having to go through a 1+ year grant funding cycle before work can commence. This flexibility results in a very significant potential, if utilized well, to accelerate the development of research findings of policy relevance. It was nicely argued by one

of the Center Directors, that, given the large amount of money (both on the benefits and cost sides) which hinge on the regulatory decisions informed by the Centers research, there is a strong societal imperative for maximum speed in the generation of policy-relevant research results. Of the funding mechanisms available to EPA, the Centers approach appears to be the best mechanism for achieving this speed.

Another value-added activity originating from the Centers Program is the very thoughtful and carefully planned use of pre-existing data sets in follow-up analyses. It is likely that this process first began at the time that the original Centers proposals were prepared, and it is a particular benefit of the Centers approach that these follow-up analyses have now been completed. Under a traditional individual grant-based approach, it is less likely that these additional analyses would have been completed due to the time pressures on investigators to continually apply for additional funding. A further example of this value-added activity is the planned, pooled analysis of the Southern California CHS and the 24-Cities Study. While both studies have evaluated lung function and lung function growth, the CHS was focused on the impact of mobile sources, while the 24-Cities Study was focused on the acid aerosol/sulfate Eastern air pollution mixture, thus offering the opportunity to compare health effects in areas with substantially different air quality.

Another related advantage of a Centers-based approach is the ability to pursue lines of pilot investigation which, due either to their exploratory nature or to their relatively small scale, would not be easily fundable as stand-alone grants. The Centers mechanism has made it possible to investigate a variety of important epidemiologic questions based on new analyses of existing databases. Most, though not all, of the Centers have been very effective in exploiting these unique advantages of nimbleness and flexibility in maximizing their investments in epidemiologic work.

Have the Centers made a difference in the conduct of epidemiologic research? The answer is clearly "Yes", in part, because investigators have been free to continue pursuing promising leads without having to apply for new grants. They have been able to follow new directions, that might not necessarily have obtained funding in a competitive process. Examples include the following:

1. Center funding has allowed the Harvard Center to refine and explore alternative methods, as well as the application of the methods to alternative data sets, in its research on harvesting and threshold/exposure response. The preparation, review, and awarding of proposals/contracts could have delayed the process significantly.
2. The Centers Program has enabled the Southern California Center to conduct extended analyses of the CHS as new hypotheses are introduced.
3. The Centers mechanism enables researchers to quickly address a new subject; e.g., the association between diabetes and PM pursued by the Harvard Center and the study of the association between reproductive effects and air pollution planned by the Southern California Center.

4. The Centers Program enables researchers to replicate quickly studies in one geographic area in different areas; e.g., activities at the Northwest Center. Comparisons of results from similar studies in different geographic regions can clearly provide insights into the underlying mechanisms.
5. The Centers are planning a workshop to discuss and harmonize source apportionment methodology for use in epidemiological studies. Several epidemiological studies have evaluated source category impacts. The workshop will attempt to utilize more fully the available source appointment techniques and source signature data to evaluate the health impacts of specific sources.

Given these strong advantages, there are several ways in which the work of Centers might be further enhanced:

1. In view of the public health significance of long-term effects on survival, the effort within and among the Centers to provide new insights is still somewhat limited. There has also been relatively little work on the development of appropriate monitoring strategies/methodologies (statistical designs, assessment of study design efficiency, sampling method development) for long-term studies. Without these developments it is likely that continued analysis of long-term impacts or the planning of future chronic effects studies will remain opportunistic -- relying primarily on existing data such as the AIRS data or possibly the speciation network data. Although the budgets of the Centers seem large, those budgets are necessarily divided into many pieces in order to achieve the multi-disciplinary character that is a hallmark of the Centers. As a result, there is generally not a sufficiently large amount of money available for mounting a *de-novo*, stand-alone epidemiology study, which can be quite expensive.

Nonetheless, there are several examples of work underway in this important area. The Harvard Six Cities Study follow-up has been updated, and there has been mention that the Northwest Center might investigate another cohort. There are also two examples of ongoing or completed studies on school children (the Southern California and Harvard Centers) that will use sophisticated exposure assessment techniques.

In sum, it seems that the Centers program is ideally suited to exchange and harmonize exposure assessment efforts in the long-term studies.

2. It is important to note there is another potential side to rapid implementation of changes in research; i.e., a risk of poor quality if the peer review of interim research results and decisions is sped up too much. It is clear that informal peer review occurs in the Centers via their Science Advisory Committees (SACs). Continued attention to and enhancement of these reviews by the SACs would help to ensure that the quality of research continues to be high and is perceived to be so by the public.

3. It would be useful to see enhanced interaction between the research conducted at the Centers and ongoing intensive air quality monitoring efforts, such as those at the Agency's

supersites and others. (The Southern California Center provides a model of how this might be done. Interaction with NARSTO would provide other opportunities.) The detailed air quality data collected at these sites should be utilized as much as possible by the epidemiology community. In general, it will be important for the various Centers to consider the chemical composition, as well as size, of constituents of PM in their research designs.

b. Monitoring and Air Chemistry

There are several examples of research progress that has been made as part of the Centers program that would have been unlikely to occur or would have been less beneficial to the overall research effort in the absence of such a program.

One example is the planned workshop (described in the previous section) to discuss and harmonize source apportionment methodology for use in epidemiological studies.

Many of the Centers are making use of concentrated ambient particles for toxicological studies. The extent of integration of this methodology, including the detailed characterization of particle speciation, has been thorough under the Centers program. There has been evidence of an iterative process in which improved particle characterization from monitoring and epidemiological field studies have informed toxicological studies. While it is premature to have expected a second iterative step in which the results of these toxicological investigations have contributed to the development of new epidemiological studies, such a positive feedback of information can be anticipated in the future.

As a result of specific Center needs, there have been initial developments of new sampling techniques and extensive integration of state-of-the-art existing measurement techniques in epidemiological, toxicological, and exposure investigations. Examples of new methods and their immediate and extensive use in Centers research are the use of the multi-pollutant personal sampler (a device worn by participants to measure total personal exposure) in several of the panel studies, the development of the ultrafine particle concentrator, the development of new methods to measure methoxyphenols as markers of wood smoke combustion, and the development of a new personal sampling method for temperature-resolved carbon fractions.

Another interesting development that exemplifies the flexibility inherent in the Centers program is the increased emphasis on spatial variability within the Southern California and Northwest Centers. This new research direction builds upon studies conducted in Europe investigating the impact of proximity to traffic sources and adds a potentially important new area of emphasis for epidemiological studies which has not been considered in the time series studies or the main US cohort studies.

Additional areas in which the Centers program has made contributions that would not have been made otherwise include the following:

1. Validation studies

The Centers Program makes it possible to conduct specific short-term studies

designed to validate or test methodology used in larger studies or to address specific research questions that have arisen in larger studies. Even if such short-term studies were to be contemplated under a more traditional investigator-initiated research program, they would be unlikely to be supported. Examples of such validation studies include a) the assessment of source impacts and housing factors (ventilation) on effects estimates of the PM-hospital admissions relationship from the NMMAPS study and more detailed evaluation of the harvesting phenomenon and b) the plan to replicate the multi-pollutant exposure sampling in an additional location, beyond Baltimore where the initial investigation was performed

2. Pilot studies

Centers funding makes it more possible to design, develop, and test new methodologies or to explore innovative hypotheses, activities which would likely be less successful in an investigator-initiated grant environment. An example of this type of study is the Southern California Center's work on quinones and other organic compounds that are precursors to the development of reactive oxygen species. This effort has involved the development of new sampling and analytical methods to link exposure assessment with toxicological investigations.

c. Exposure assessment

To date, exposure assessment activities have focused in four areas: 1) investigations of the relationship between personal exposure to and ambient concentrations of PM; 2) resolving the contributions to personal PM from indoor sources and infiltration from ambient particles into indoor airspaces; 3) analysis of specific chemical components of personal PM that could explain observed health effects; and 4) measurements of personal exposure to mixtures of PM and gaseous pollutants. These research activities, as well as others at the PM Centers, are integrated with research efforts in epidemiology, toxicology, etc., which is a major strength of the PM Centers approach. Another strength is that the research, while generally integrated across Centers, makes use of Center-specific environmental and lifestyle characteristics that may provide further clues on exposure-response relationships. The recognition and exploitation of these differences and similarities in a more integrated fashion is another strength of the PM Centers.

The exposure research approaches and findings to date are not novel. Some investigations have confirmed prior reports by non-Center investigators, and other investigations have applied methods developed and used by non-Center investigators to their specific area. Still others have used instrumentation developed by Center investigators prior to the establishment of the centers. However, the advantage of exposure research at the Centers is that the findings have immediacy in terms of feeding into health-related studies because of the multi-disciplinary principles upon which the Centers undertake their research activities. Information sharing and Center-specific internal cross-disciplinary interaction and coordination in exposure research are obvious and very strong; e.g., the references to the NMMAPS and Baltimore studies in the previous subsection.

The Centers program is clearly allowing the Centers to improve the exposure assessment component of the epidemiology studies. It cannot be stressed enough that this is where important new insights will emerge that will help policy makers eventually to identify which

particle components, attributes, and sources are important in explaining the health effects seen in epidemiologic studies. The benefits could still be greater if the Centers were to put more effort into applying the same tools to all relevant particle exposure measurements; e.g., assess spatial variability on the regional and local scale for secondary components, ultra-fine particles (UFP), traffic-related components etc.

Each of the current Centers has a research project related to exposure of various populations to environmental levels of PM and co-pollutants. At the same time, not all Centers have as their primary goal conducting a large scale population study. This is probably a good approach since the cost of such studies requires the diversion of significant Center resources. However, these are important studies, and the cost of such studies may require funding by a different mechanism (perhaps a cooperative agreement) in order to take advantage of resources available from the Agency, the National Institute of Environmental Health Sciences (NIEHS), the Centers for Diseases Control and Prevention (CDC), the National Institute of Heart, Lung, and Blood Institute (NHLBI), and other national agencies.

The Centers program provides the opportunity for exposure scientists to share results and hypotheses in forums that can effectively disseminate important ideas and results to members of multiple disciplines as diverse as toxicology, epidemiology, and clinical sciences. The exposure scientists provide the link between the epidemiology and toxicology studies with findings of better indicators or metrics of exposure in populations at risk, which can augment or replace specific PM components in toxicology evaluations; e.g organic carbon and ultrafine aerosols, instead of elemental carbon and non-size segregated aerosols that were originally used to examine mechanisms of exposure and response. For example, in the current Centers program this integration is manifested by panel studies of exposure and health outcomes. Instead of conducting a single RO1-based exposure panel study that would produce population exposure intensities and profiles, the Centers provide the opportunity to augment the usefulness of these measurements by integrating them with health outcomes research. In an RO1-based approach, a new grant application targeted at health outcomes would probably have to be submitted based on the results on the prior RO1 exposure study. Thus, to meet the needs of the national PM research program, the Centers concept provides a more effective use of time and resources.

It is too early in the first funding cycle of the Centers to see clear examples of feedback loops between exposure and health-related studies that change the direction of the investigation in the various disciplines. At this time, the exposure assessment research efforts are guided by the need to reduce uncertainty in specific areas of personal and community exposure to PM in order to reduce uncertainties in health investigations. However, there are activities that may result in redirection of health effects studies because of exposure research findings; e.g., the finding of quinones and related compound concentration gradients.

It would seem that the exposure-related research undertaken to date, with very few exceptions of still uncertain significance, would probably have been carried out without the Centers. However, efficiencies in the timeliness of the research and the application of the results are hallmarks of the Centers program and would be unlikely to be achieved otherwise. It is important also to recognize that there is a very large body of research on exposure to PM outside

the Centers. It is not clear that the Centers are as active in the incorporation of non-Center research they are with intra- and inter-Center findings.

One approach to incorporating the non-Center findings would be for the PM Centers program to organize an assessment of the state-of-exposure-science and related disciplines that includes work being conducted both inside and outside of the Program. Such periodic examinations would help the Centers in planning and conducting their research. There are other programs in the US, Europe, and elsewhere that have and continue to accumulate information and results that can assist in planning Centers-based activities and in the development of external collaborations.

Finally, although PM characterization activities are described as being directed at physical and chemical characteristics, most of the focus is on chemical composition size distribution. There are some initiatives to look at other attributes, surface characteristics being a particularly important one. The Centers program is uniquely positioned to provide a “whole picture” evaluation of the exposure-effects continuum. This approach needs to be enhanced both in the PM characterization/exposure end of the paradigm and in the integration of the multiplicity of health effects to explain alterations in physiology that can lead to early death and disease aggravation.

d. Toxicology

Among the most promising aspects of the PM Centers program is the focus on understanding the biological plausibility and mechanisms, dosimetry, and further identification of the toxic components of PM. Addressing these issues, in the context of how epidemiological, exposure, aerosol, and other sciences are woven into the picture, increases the likelihood of accurately assessing the plausibility of proposed hypotheses and mechanisms. Furthermore, the collective presence of elite scientists within and across the Centers seems to promote a considered and consistent approach to testing and validating hypotheses. The intra- and inter-Center attention on new discoveries and findings appears to force higher quality of product. This implied peer presence and peer review increases the level of confidence in results reported from the Center studies as a whole.

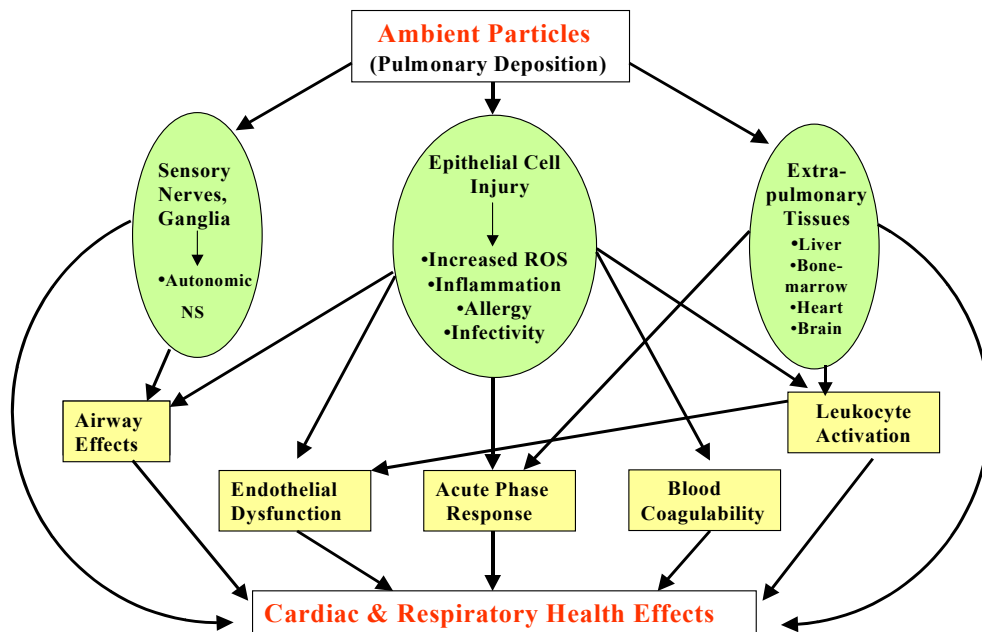
The Centers, through a series of animal and human clinical experiments, have been effective in evaluating hypotheses related to inflammation and immunity and cardiovascular effects due to exposure to PM at ambient levels. The inflammation pathway has been linked to both acute and chronic effects. In order to test and evaluate the validity of observed results, multiple Centers collaborated, through controlled interactive experiments and shared protocols, in testing, for example, the effects of different particle size fractions and conducting inter-species comparisons. They have also begun addressing factors of susceptibility, such as aging. The outcome of this research has been a remarkable consistency and continuity in the observed effects that appear to lead to unified hypotheses on mechanisms and pathways. This weight-of-evidence and the need for internal consistency in understanding the observed effects is a significant contribution of the PM Centers.

Ongoing and future efforts directed at further deciphering mechanisms for acute effects appear promising and responsive to one of the critical challenges to the existing modifications to the PM standard. In the future the Centers will likely address chronic and subchronic effects that have previously been reported in epidemiological literature. Also, pilot studies are planned to address dosimetry issues and hypotheses. Addressing most of these areas has required significant innovation and employment of study designs and technologies that previously had not been applied to these areas. Such innovation is another major attribute of a Center-based program.

It appears that preparation for this review provided a significant stimulus for inter-Center collaborations in developing and evaluating biological and toxicological hypotheses. During the course of this review, the Panel learned that the Center Directors are mapping out meaningful next steps for enhancing the collective understanding and interpretations of results reported to date. Since PM and its components can have significant regional characteristics, it is important for the Centers to consider exchange and further evaluations of the PM itself. The relevance of PM composition and related source attribution are critical to our understanding of the reported results.

Figure 1, taken from the presentation of one of the Center Directors, Dr. Oberdorster, provides a unifying patho-physiological scheme for conceptualizing the mechanisms of PM effects.

Biological Mechanisms of PM₁₀ From Exposure to Effects



This integrative picture was developed through the collaborative discussions across the Centers and has provided a roadmap for larger toxicology community; hence, it is a significant contribution. The central role of oxidative stress is being investigated in all Centers as shown in Figure 2, also taken from Dr. Oberdorster's presentation.

Figure 2

Examples of a Common Theme:
Oxidative Stress

<u>Harvard:</u>	<i>CAPs</i>	————→	<i>coronary events</i>		
<u>New York:</u>	<i>Transition metals on PM</i>	————→	<i>infectivity</i>		
<u>Northwest:</u>	<i>PM</i>	————→	<i>asthma aggravation</i>		
<u>Rochester:</u>	<i>UFP</i>	————→	<i>pulm. inflam.</i>	————→	<i>endoth. dysf.; age</i>
<u>So. California:</u>	<i>Quinones, ketones on PM</i>	————→	<i>release of ROS</i>		

Another example of collaborative efforts that have been strengthened through the Centers is the rapid initiation, development, and review of a protocol for subchronic CAPs exposure studies in mice, subsequently leading to a chronic study. Such studies were not envisioned in the original RFA. However, through inter-Center discussions and review, these studies were identified as critical to furthering understanding of the mechanism of particle toxicity. The draft protocols have been circulated for comment and refinement through the Center Directors, with the goal of optimizing the protocol. The review process has included comments and suggestions from Agency scientists as well, in keeping with the Centers' outreach to the scientific community.

e. Science Management

The Centers program has allowed for the development of a critical mass of technical PM expertise in interdisciplinary research at and between the individual Centers. By design, the Program forces interdisciplinary planning and coordination at the inception of study design, rather than as an afterthought, thus leveraging the value of interdisciplinary research as a whole. In concept, when epidemiologists, exposure experts, aerosol scientists, toxicologists, physiologists, and other scientists engage a problem collectively, there is a higher likelihood of a cohesive approach to the research than would result from a simple assemblage of individually conducted research projects. One of the PM Centers' greatest successes to date is its serving as a forcing function to promote this multi-disciplinary interaction from the ground up. In doing so, the Centers program has created a network of scientific expertise that has the potential of effecting a broad, balanced approach that also includes an imbedded mechanism of self-critical peer-review.

Judging from information in the integrated report from the Center Directors, another attribute of the Center approach is that the time for hypothesis generation and experimental design has been decreased, with the added advantage that hypotheses have been vetted before actual laboratory studies have begun. While this aspect may not have played a major role in the programs to date, the effect is likely to be greater in the future when several new and innovative studies are envisioned.

An investment of approximately \$1.5M/year/Center, while significant in total dollars, should be viewed in the context of the types of studies necessary to advance this area. One panel study of exposure/health alone can cost well over a \$1M. If instead of using a Centers-based approach, individual grants approach had been used, either 3-5 investigators would have been forced to collaborate (always a technical and administrative challenge), or the Agency would have had to establish and prescribe research area priorities over the five-year period; e.g., toxicology, first, and exposure studies, next. A research management approach, like the Centers program, that has the capability of planning for both types of studies at the same time, holds the promise of a superior outcome. In addition, this investment has been and will be advantageous to the Agency because of the leveraging opportunities that arise from the Centers themselves, as well as from other on-going research and support provided by other agencies and funding organizations.

On the basis of reviewing the report from the Center Directors that was prepared for the Panel, it would seem prudent to extend this program beyond FY04, to capitalize on the investment made to date, and to take advantage of the apparent time efficiency that seems to be demonstrated.

The request for the current SAB review seems to have motivated the type of inter-Center collaboration and outreach that the Agency was hoping to achieve. This result argues for instituting a requirement for an integrated annual report. It is important, however, that the Center Program not become "an entitlement program" for certain institutions; rather, all institutions should have to compete on their individual merits for continued funding beyond FY04.

Based on the written background materials provided, there does appear to be some disparity in the progress of individual Centers. Without an actual site visit and further interactions with the individual Centers and their SACs, it is difficult to judge their individual contributions and their progress relative to target. Such a site-specific examination is beyond the scope of this particular review.

Because investigators at these particular Centers have a history of leadership in PM and health effects research, their reputations were well-known prior to the Centers program. However, the Centers concept has fostered additional development of a critical mass in interdisciplinary research that has germinated new collaborations from others within the research community, adding to the existing visibility and status of each of the Centers. As Centers, they appear to render consistency to research in PM, which has generated additional confidence in the results they report.

There is a concern, however, that if research is conducted outside the Center framework, then that work may be ignored or deemed to be less important, and consequently not as well received. If their success were to lead to an attitude of exclusivity, then the Centers would run the risk of becoming insular and oblivious to advances made elsewhere, some of which could have implications to their own work. These concerns should be monitored, noting that some extra-Center interactions can be promoted through such devices as symposia and workshops.

The Centers also provide excellent educational opportunities, allowing for the training of young investigators in an atmosphere of interdisciplinary research. Those who are trained outside and across the traditional disciplinary silos that have marked much of traditional training and who are accustomed to collaborative research are more likely to transfer this understanding to their future work. This birthing of a "next generation" of scientists is an important product of the PM Centers Program that can potentially change the way research is conducted in the future in all areas of environmental science.

The Centers have provided significant flexibility in which higher risk research activities, such as method development, validation, and pilot studies can be accommodated. This flexibility has led to the development of innovative methods, designs, and technologies. Inter-Center transfers and sharing of personnel and technology have provided an added opportunity to validate and test these innovations. These transfers have also extended to extra-Center collaborations and have the potential for broader application. It is important to encourage and further enhance this important attribute and contribution of the Centers program in the next phase of the program. Some examples include the following:

- 1) New statistical methods for design of studies and analyses of results from epidemiological and exposure studies.
- 2) Coarse, fine, and ultrafine mobile concentrators for field use.
- 3) Coarse, fine, and ultrafine biological sampling techniques for *in vitro* mechanistic studies.
- 4) Inhalation toxicology trailers for field studies through the Los Angeles Basin (Human and animal trailers).
- 5) Particle instrumentation unit for field PM characterization.

f. Policy-Relevant Science

The fundamental reasons for initiating the PM Center research program sprang from the science/policy debate that took place during the last review of the PM-NAAQS review and the questions raised by the Clean Air Scientific Advisory Committee (CASAC) during its deliberations. It was envisioned that an extensive research effort by the Agency would clarify and resolve the issues, provide answers to questions raised, and assist in the next round of PM-NAAQS review.

It appears that key areas of concerns that were expressed during the last review of PM-NAAQS -- in particular, dose-response relationships, existence or lack of threshold for PM effects, and issues related to harvesting -- that are central to future policy direction and regulations, are being addressed by at least some parts of the PM Centers program, as well as by

investigators outside the program. Because of the critical nature and implications for future policy in these matters, it would be useful if these findings were replicated and validated by other investigators, inside or outside the Centers program, *per se*.

There have been many projects started to address policy-relevant questions. At this stage, the projects directly relevant to specific standard-setting questions have included continuation and follow-up of studies underway prior to the establishment of the Centers program; e.g., harvesting, dose response, follow-up of existing cohorts, some controlled human exposure work, and experiments on underlying biological questions, such as mechanisms of cardiac effects. The regular interaction within and between the Centers appears to have refined these efforts. Although some portion of the work may have been possible with different funding approaches, there have been clear benefits from the Centers-based approach, especially in the toxicology and epidemiology interactions and its implications for the work on mechanisms.

The PM Centers research program has already produced some findings of policy significance. For example, the addition of work from the Centers to other studies suggests the absence of a threshold for PM effects, a finding which raises an important policy issue. Another important observation is the suggestion by the Rochester Center that ultrafine PM has effects distinct from those attributable to PM₁₀ and/or PM_{2.5}. Also, preliminary findings from the PM Centers program support or expand upon previous findings that motor vehicle emissions appear to contribute significantly to PM health effects, that NO_x levels are associated with lung function changes in children, and that the organic portion of PM may be responsible for some of the PM effects. Such information raises some key policy and controls-related questions, such as how to reduce exposure to the most toxic PM fractions.

Although there are substantial and innovative starts at examining individual PM sources and components (e.g. ultra-fines, metals, and quinones) at different Centers, there is less coherence in how the effects of exposures a) to emissions from different sources and b) to different components and sizes of particles will be systematically compared, which is an important forward-looking policy question. To date, although some consistent findings have been reported, some intriguing findings that are not consistent between the Centers need to be followed explored further. It will be critical for policy makers to understand the reasons for these differences, if they are real. In addition, the Agency should take the lead in sorting out these differences by working actively with the SACs and the Center Directors. In this regard, it is worthwhile considering the option of creating an overarching mechanism to advise all of the Centers and to coordinate insights in cases of seemingly conflicting data.

g. Multi-disciplinary and Inter-Center Integration

The STAR program is built upon the idea that the results must provide value-added to the information that is being generated by the Agency, other stakeholders, and individual investigators. It may be necessary to find metrics of success that go beyond scientific publications derived from individual studies. The Centers' research impact value compared to contributions generated via alternative funding mechanisms, will be an important barometer of success. Again, the degree to which the Centers can provide answers to multi-disciplinary issues, as well as provide key changes in direction, will be very important indications that the

Center's program did make a difference. An important measure of success for this program is the presentation of results and conclusions that will improve the scientific basis for the standard and provide direction for implementation of control strategies by Agency program offices.

The Center Directors report prepared for this review reflect a good start at inter-Center collaboration. It will likely take at least another year to assess the full impact of the anticipated increases in interaction. Namely, will the intra- and inter-Centers interactions continue, leading to better science or fuller consolidation of the science that has been learned? Such a relationship will be a key metric of success. Will "Centered-ness" achieve new exploratory research that continues along multi-disciplinary lines, or will the Centers consolidate their thinking to test a single or a limited number of hypotheses? If the tendency is toward the latter, then the effectiveness of the Centers approach may be lost, or the number of Centers could be reduced or augmented to address new problems that would not be explored based upon the disciplines that comprise the current individual Centers. In terms of other stakeholders, it is not clear that if the way in which the Centers were established allows much flexibility for outreach to other scientists, except at the individual investigator level. Fortunately, inter-organizational efforts are usually most effectively started by individual investigators. The members of the Centers have a history of success with inter-organizational collaborations, and their success over the course of the next year may provide information about what kinds of formal outreach programs may be required for a future RFA.

There is no clear path in the current design of the Centers program that integrates major research findings into the development of an effective control strategy to protect public health. A future RFA needs to clearly incorporate this important task to ensure that the results are directed towards these concrete endpoints.

The previous RFA emphasized the need to a) set up a Center's clearinghouse function in order to share of its research information with other entities and b) develop methods of obtaining valuable information from other sources. These objectives should be a part of any future RFA, and the current Centers need to be encouraged to move in that direction.

Two of the major attributes that should characterize the Centers are synergism and broader exploration of the science, not necessarily premature consensus building among the Centers. These concepts could be effectively developed through annual workshops organized by the Centers. The workshop on cardiac effects conducted last year and the proposed workshop on receptor modeling are examples of how a forward-thinking Centers program can move the entire PM research field forward effectively.

2.2.2 Communications

Q3: How successful are Centers in communicating their findings to the public and specifically, to those who directly use their research? Is it clear that the work has been supported by the PM Centers program?

At this early stage, it is, understandably, difficult to judge how well the Centers have succeeded in establishing effective communications. It is noteworthy that quite a few publications have been generated to date that form a sound baseline for the direction of future efforts in the Centers program and for research in the broader research community. Many of the Centers appear to have used the popular media and community outreach effectively to publicize their preliminary findings and to respond to inquiries. It also appears that they have assembled multi-stakeholder SACs to ensure a flow of information in various sectors of the community.

It may be that with the infrastructure of the Centers the universities were better able to feature this program as a community benefit, not singling out an individual investigator, but as providing public health information to the media and public who have interests or questions about PM issues. Since it is difficult to provide such a function in a cost-effective manner with individual research grants, including this requirement in the RFA has reaped significant benefits. It has also provided an administrative framework that could be utilized to broaden communication activities to other groups; e.g. the regulated community.

One area in which there may be an opportunity for further improvement is the possibility of a strategic communication plan across the Centers that would address the multiple audiences that are targets for this information, including the scientific community. To date, Center-based technical meetings have been planned with a year or so lag time, similar to what would happen with individual investigator-focused grants. There may be advantages to thinking more broadly about this problem, especially if the directions of the research continue and the findings from these studies have the expected significant implications on public health. In this regard, making the annual Centers meeting an open public scientific meeting would be especially valuable in improving communication with the greater scientific community. To further enhance communication, the Centers should maintain strong contacts with state and local air agencies representatives, if that is not already the case.

2.2.3 Inter-Center interaction

Q4: How, if at all, does a PM research centers program facilitate agreement or consensus on protocols or procedures to enable more direct comparison of results among research institutions or centers?

There is evidence that the Centers appreciate the need for harmonization of protocols, and there have been some attempts to do this. Achieving this end, however, is a daunting task both organizationally and psychologically, since scientists like to adhere to their own pet methods. If experiments are under way, then it is not a good idea to try and get workers to change their protocols. However, for new studies or extensions of existing studies some consideration of alternative, harmonized protocols could be advantageous. A centrally held database of protocols would be an efficient and effective means of allowing experimenters to see what protocols are in use or under consideration at other Centers. Periodic, joint meetings that include discussion of methodology issues could also be undertaken.

Probably the best example to date of inter-Center interaction is the Rochester Center's workshop on the cardiovascular effects associated with air pollution: potential mechanisms and methods of testing. The workshop culminated in an excellent report that contained a list of the various methodologies recommended and the parameters they assessed. This effort could serve as a model for workshops on other issues, such as particle size measurement, particle composition measurement, *in vitro* toxicology models, and animal models.

There is a clear need for and benefit from increased inter-Center interaction, specifically in the new panel studies being undertaken at all of the Centers. These studies mostly focus on cardiovascular and respiratory endpoints and are generally of a small scale. There is much effort in these studies to obtain detailed exposure data, as well as detailed health endpoint data as described above. Such collaboration/interaction is an advantage both, in principle and -- as demonstrated in the Centers program-- in fact. However, there is a potential problem with statistical power and with generalizability arising from a collection of individual studies. Panel studies limited to several hundreds of observations are susceptible to producing "noisy" associations, which may vary from study to study or from study period to study period. Also, because of the level of detail in the exposure and health endpoint assessments, there are many associations to investigate, which increases the probability of chance associations, especially in size-limited studies. The Centers program should stimulate and facilitate collaboration within and between the five Centers, with the goal of harmonizing designs, methods of measurement, and analysis of these studies. The foreseeable result would be a unified interpretation of the results of the panel studies that would be much more rigorous than a post-hoc, meta-analysis of completed studies would allow.

At the same time, it should be recalled that diversity of protocols can be seen as a strength since huge amounts of data showing an effect using a single approach may not be as powerful, or as persuasive, as decent amounts of data showing similar effects using different approaches.

Among the more general opportunities for enhancing this cross-Center work are the following:

- a. The possible publication of a newsletter that would keep running lists of methods being used and allow the Centers to identify areas of protocol exchange and harmonization.
- b. More PM Center workshops like the one organized by the Rochester Center where methods can be exchanged and opportunities for protocol exchange and harmonization can be identified.

- c. Attempts to develop reference materials, like the Southern California Centers efforts on fine PM, which is an excellent idea when investigating a toxin so variable as PM, especially for *in vitro* toxicology and animal studies.
- d. Development of a centrally held, easily accessible database of downloadable pdf files of protocols.

2.2.4 Leveraging

Q5: How, if at all, does a PM research centers program leverage or maximize use of resources through sharing expensive equipment, samples, data, etc.?

Each of the Centers -- and each of the investigators within the Center -- has specific strengths in resources and expertise. There are two types of interaction that maximize resource use: intra- and inter-Center interactions. There are many examples of intra-Center interaction; e.g., common protocols and shared use of equipment across projects within a Center. One clear example is the Rochester Center's common use of cardiac analysis, flow cytometers, particle generation cores, and ultrafine concentrators across different studies.

There are also examples of specific strengths of one Center (e.g. sampling and analytical tools and equipment) being made available to others through cross-Center collaboration. To mention only three, the Harvard Center developed the concentrator that will be tested/used by the Rochester Center, the Southern California Center has given PM samples to investigators at other Centers, and the NYU Center is gaining input from other Centers as it prepares for testing in mice.

In addition, the PM Centers are identified centers of PM expertise that allow them to attract additional resources to fund other studies that are closely related to the goals of the PM Centers Program.

However, there are still additional opportunities to enhance inter-Center utilization of resources and expertise. Even though multi-disciplinary in nature, no Center can be equally excellent in all areas. Such situations may not be even desirable, because it may not be an efficient use of resources. It is important that the Centers recognize their individual areas of strengths and make those available to others. This realization would increase cross-Center collaborations in a significant way. Inter-Center collaboration is a difficult issue for inclusion in a future RFA because each applicant develops his or her own independent research program. There should be a mechanism (perhaps involving the SACs) to facilitate/insure synergistic cross-linking among the personnel and hardware/software assets of the different Centers. This coordinating effort must not interfere with the completion of the science proposed and developed by each Center.

2.2.5 Perception and visibility

*Q6: How is the program perceived within and outside the research community?
Does a research center have greater visibility, and if so, what is the impact?*

As a novel approach for funding research, the PM Centers Program is being closely watched on a number of fronts. The significant percentage of the Agency's total PM research budget devoted to the Centers is additional motivation to observe the workings of the Centers closely. Finally, the importance of the issue with which the Centers deal (i.e., the effects of PM in our nation's air) insures considerable attention from a range of interested and affected parties.

Because each of these particular Centers has a history of leadership in PM and health effects research, widespread knowledge of their work and their reputation preceded the Centers Program, *per se*. However, the Centers concept has fostered the development of a critical mass in interdisciplinary research that has spawned new collaborations from others within the research community, adding to the existing visibility and status of each of the Centers. As Centers, they appear to be maintaining the consistent quality in their research endeavors, which has generated additional confidence in the results they report.

Beyond visibility in the scientific community, in general, the Centers Program has provided excellent educational opportunities, allowing for the training of young investigators in a non-traditional interdisciplinary manner. Such motivated young people, equipped with technical skills and an appreciation of what it takes to attack a complex environmental problem will be a valuable resource for the future.

One area for attention, however, may be that if research is conducted outside the Center framework, it may be ignored or deemed to be less important, and consequently not as well received. In their exclusivity, the Centers also would run the risk of becoming insular and oblivious to advances made elsewhere, some of which may have implications to their own work. These are issues that should be monitored and some extra-Center interactions can be promoted through symposia and workshops.

3. FINDINGS AND RECOMMENDATIONS

1. The PM Centers Program has both a) produced benefits beyond those normally found in individual investigator-initiated grants and b) is likely to continue to provide such benefits through to the end of its current funding cycle. Overall, the Panel found that the program merits continuation beyond FY04 -- through a new fully-competitive round of applications -- as one part of a diverse PM research portfolio at the Agency.
2. The Panel identified several specific advantages that the Centers approach offers over other traditional research mechanisms, including enhanced flexibility and adaptability leading to improved timeliness, ability to conduct higher-risk pilot and validation efforts, study designs enhanced by intra-center multi-disciplinary integration, and improved leveraging of the Agency's and the Centers' research resources, among others.
3. The Panel identified several ways in which a new round of Center grants could be enhanced, either by expanding upon activities already underway or by undertaking new efforts. Importantly, the Panel noted that while there are evident benefits of integration within and across Centers, there are also potential challenges to insure that the work of the Centers does not become isolated from that of other researchers within the Agency and in the academic community. Key enhancements include the following:
 - a. Continued attention in a new request for applications (RFA) to focusing the Centers' efforts on the most critical PM needs, as determined at that time in reviews of research progress and needs by the National Research Council and US EPA
 - b. The development of an informal, but overarching, mechanism of scientific advice to the program
 - c. Enhanced opportunities for cross-fertilization of ideas with EPA intramural researchers and the broader extramural community
 - d. Enhanced interaction between the research conducted at the Centers and ongoing intensive air quality monitoring efforts, such as those at the Agency's supersites and others
 - e. The provision of systems and resources from the start for inter-center integration efforts.

APPENDIX A - ACRONYMS

Agency	US Environmental Protection Agency
AIRS	Aerometric Information Retrieval System
CAA	Clean Air Act
CAAA	Clean Air Act Amendments
CAPs	Concentrated Ambient Particles
CASAC	Clean Air Scientific Advisory Committee
CDC	Centers for Disease Control and Prevention
CHS	Children's Health Study (Southern California PM Research Center)
EPRI	Electric Power Research Institute
FY	Fiscal Year
HEI	Health Effects Institute
MMD	Mass median diameter
NAAQS	National Ambient Air Quality Standards
NAS	National Academy of Sciences
NCER	National Center for Environmental Research
NHLBI	National Heart, Blood, and Lung Institute
NIEHS	National Institute of Environmental Health Sciences
NMMAAPS	National Morbidity, Mortality, and Air Pollution Study
NRC	National Research Council
ORD	Office of Research and Development
PM	Particulate Matter
PM _{2.5}	Particulate Matter in the range of 2.5-10 micron
PM ₁₀	Particulate Matter of larger than 10 microns
RFAs	Request for Applications
RO1	Single project research grants funded by the National Institutes of Health
SAB	USEPA Science Advisory Board
SAC	Science Advisory Committees (at each of the Centers)
STAR	Science to Achieve Results
UFP	Ultra-Fine Particles

APPENDIX B

A MORE DETAILED DESCRIPTION OF THE SAB PROCESS

After receiving the Charge from the Agency in the summer of 2001, the SAB Staff initiated a process for soliciting the names of candidates whose expertise would allow them to make substantive contributions to answer the Charge questions. This solicitation included

- a. Contacting various individuals within EPA
- b. Publishing a notice in the Federal Register (Oct. 10, 2001, 51661-51662).
- c. Contacting knowledgeable SAB Members and Consultants

The process (referred to as the WIDECAST) garnered 48 names, several being mentioned by more than one source.

After further discussions with the SAB Staff and Agency personnel, the SAB Staff Director contacted Mr. Daniel Greenbaum, President of the Health Effects Institutes who agreed to serve as chair of the Panel. Having established Mr. Greenbaum's available dates to hold a face-to-face public meeting, SAB Staff contacted all of the members on the WIDECAST and, after briefly explaining about the SAB and the proposed interim review of the PM Centers, inquired as to their interest and availability.

The 14 individuals who responded positively, submitting their public curriculum, became the "Short List" of candidates. In each case, the person's curriculum vitae was used to construct a "biosketch" of the candidate that described the individual's current position and affiliation, expertise and experience in the matters at hand, experience on other advisory committees, particular association with any of the PM Centers, and sources of research funding. The biosketches were sent to the candidates for approval, after which they were posted on the SAB Website (www.epa.gov/sab) for any comments that members of the public might want to make that could help inform the final Panel selection. The SAB Staff Director made the final selections, conferring with the Panel Chair and with the Executive Committee Chair (Dr. William Glaze). Primary consideration was given to expertise that the individual brought to the Charge questions; specifically, areas of epidemiology, toxicology, exposure, science program management, and policy-relevant science. An additional consideration was the benefit of having some Panelists who were members of one or more the advisory committees associated with each of the Centers. Such "inside insight" could be valuable to Panel as they grappled with how the Centers "work" and what impact they have had or could have. One of the Panelists selected had competed unsuccessfully in the Centers RFA competition, thereby bringing another perspective to the Centers experience.

The 12-person Panel roster was announced on the SAB Website. In the days before the meeting, complications arose for one of the members who had to withdraw; hence, the final Panel of 11 Members (including the Chair).

Agency staff transmitted the review materials to the Panelists in late January, consisting of the following:

- a. Charge to the Panel
- b. “The EPA’s Particulate Matter (PM) Health Effects Research Centers Program”, prepared by the Directors and Senior Associates of the five PM Centers
- c. Response to the Charge questions, prepared by each of the PM Centers
- d. The Request for Applications (RFA) that announced the creation of PM Research Centers Program
- e. Information about Center-sponsored workshops
- f. For each of the five Centers
 - 1) Program Abstract
 - 2) Progress Report
 - 3) Publications List

On February 5, 2002 the Chair, Mr. Greenbaum, convened a conference call of the Panel to discuss

- a. The Charge
- b. The review materials
- c. Areas that the Agency and PM Center Directors should emphasize in their oral presentations
- d. Writing assignments (Lead and Associate Discussants) for the meeting.
- e. Administrative matters

No public comments on the PM Centers were received prior to the meeting nor were any presented at the meeting.

At the public meeting on February 11-12, 2002 in the SAB Conference Room (Ariel Rios 6013), the Agency presented some background material to set the context for the review. This information was followed by presentations by each of the Center Directors, who were available to answer additional questions, as needed during the course of the deliberation. Lead and Associate Discussants used their written pre-meeting draft answers to the Charge questions to initiate the discussion. They later modified these answers to reflect the sense of the entire Panel as it emerged from the discussion. The Chair led the group in a collective discussion/editing of the response to the Overall Question, drawing on material from each of the subsequent questions. At the end of the meeting, the Chair summarized the answers to the Charge questions and the major findings and recommendations.

Following the meeting, the Chair edited the draft generated by the Panel at the meeting. After circulation and comment from the Panelists, the penultimate draft was discussed on a conference call on March 27, 2002. The Panel-approved draft was sent to the SAB Executive Committee (EC) for action during a publicly accessible conference call on May 8, 2002. [At the meeting the Executive Committee approved the report, subject to final approval by designated voters,.. This report was forwarded to the Administrator on]

APPENDIX C - ABSTRACT

The PM Centers Interim Review Panel (Panel) of the US EPA Science Advisory Board (SAB) met on February 11-12, 2002 to review the Agency's PM Research Centers program as a mechanism for generating research results that can inform Agency decision-making. Its major findings and recommendations were as follows:

1. Overall, the Panel found that the program merits continuation beyond FY04 -- through a new, fully-competitive round of applications -- as one part of a diverse PM research portfolio at the Agency.
2. The Panel identified several specific advantages that the Centers approach offers over more traditional research mechanisms, including enhanced flexibility and adaptability leading to improved timeliness, ability to conduct higher-risk pilot and validation efforts, study designs enhanced by intra-center multi-disciplinary integration, and improved leveraging of the Agency's and the Centers' research resources.
3. The Panel identified several ways in which a new round of Center grants could be enhanced, either by expanding upon activities already underway or by undertaking new efforts. Importantly, the Panel noted that while there are evident benefits of integration within and across Centers, there are also challenges to insure that the work of the Centers does not become isolated from that of other researchers within the Agency and in the academic community.

Keywords: Particulate matter, PM, research, Centers, US Environmental Protection Agency