PM Research Centers: A Perspective on Their Scientific Contributions

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From their initial inception in 1999, the PM Centers have had close interactions with the EPA intramural PM research program and over time these have strengthened. EPA scientists participate in the yearly PM Center meetings; EPA scientists sit on the Scientific Advisory Committees of all the PM Centers; EPA scientists participate in joint EPA/PM Center research projects; EPA scientists and policy staff participate with the PM Centers on bi-monthly, work-in-progress web conferences; and the EPA National Program Director for Air Research participates in the PM Center Directors bimonthly conference calls and Scientific Advisory Committee meetings.

The EPA Office of Research and Development (ORD) is charged with providing research that 1) ultimately allows the Administrator to make recommendations about the need for modifying the current NAAQS standards, and 2) supports EPA's Office of Air and Radiation (OAR) in implementing the air regulatory programs. To accomplish these goals, ORD has an intramural research program and also funds academic researchers through the PM Centers Program or by individual grants funded through targeted RFAs. To allow ORD to provide the best information in the most cost effective manner, it is important that the EPA intramural and extramural programs be well coordinated.

In the case of the PM Centers, there are numerous examples of this coordination. Three such examples are detailed below:

1) The ORD intramural program has only a single epidemiologist working in the area of PM. Given the crucial importance of epidemiological studies in PM research, a decision was made to make epidemiology a major emphasis in the first RFA for the PM Centers. As hoped, the PM Centers have proven to be leaders in advancing the field of PM epidemiology. They conducted follow-up of two major long term studies of air pollution, have been leaders in defining populations that are susceptible to PM, have provided important information about the utility of personal monitoring in epidemiological panel studies, have played a leading role in defining near-road exposures as of particular concern, and have had several papers cited as key references in the OAR Staff Paper. In this instance, the PM Centers filled a critical data gap not addressed by the ORD intramural program.

2) PM health effects appear to be driven much more strongly by cardiovascular changes than respiratory changes. However, at the inception of the current PM Centers, the ORD intramural program had (and still has) very little in the way of cardiovascular expertise. Making this an area of emphasis in the PM Centers accomplished two goals: it brought new expertise into the area of PM cardiovascular research because the PM Centers were able to attract scientists with expertise

[1] Dr. Robert Devlin has had an opportunity to closely observe all the PM Centers since their inception and is in a position to offer an informed opinion as to contributions of the PM Centers from the point of view of an EPA scientist.

in this field who had not previously considered doing research on health effects of PM; and it allowed formal opportunities for ORD scientists to interact and learn new technologies from these investigators. ORD and NIEHS also issued a joint RFA that encouraged the influx of cardiovascular scientists into the area of PM through the use of RO1 type grants. Scientists from the PM Centers have regularly participated and exchanged views in investigators' meetings with these cardiovascular grantees and other invited experts.

3) One of the strengths of the ORD intramural health effects program is clinical research. ORD scientists have provided key controlled human exposure studies in support of NAAQS standards for more than 30 years. However, the transition from studying gaseous pollutants such as ozone to studying particulate pollution presented a technological challenge of exposing animals or humans to complex particles whose chemistry and concentration differs every day. The PM Centers developed technology to allow controlled exposure to ultrafine, fine, or coarse particles. Using this technology, ORD and Center investigators have worked together closely to develop identical exposure facilities and to use a common set of health end points that are measured at all sites. Additionally, some samples collected at all the sites will be measured at a single location to better standardize data. The ability to closely align geographically dispersed programs is one of the strengths of the PM Centers program.

ORD was fortunate to have several strong applicants respond to the RFAs for PM Centers. Consequently all of the Centers are staffed with a core of internationally renowned scientists who have consistently provided cutting edge and high quality research throughout their careers. As might be expected from such a group, the Centers have been leaders in several areas of PM research. A few examples are described below, though they certainly do not represent the entirety of PM Center scientific leadership accomplishments:

1) Gene Environment Interactions

It has become increasingly clear that the presence of specific genetic polymorphisms or epigenetic factors can greatly influence the response of an individual to environmental toxicants. The PM Centers have been leaders in the field of using this technology to identify specific SNPs or factors that render people susceptible to PM. Additionally they have used in vitro approaches to better understand the mechanisms by which specific polymorphisms cause susceptibility. The initial seminal publications from the Centers have also stimulated other researchers to expand the range of genes that may impact the response of a person to PM.

2) Ultrafine Particles

Since the current EPA PM standards are based on mass in specific size ranges, they do not address very small particles that have virtually no mass but do have a large surface area. The PM Centers have been world leaders in defining health effects associated with exposure to ultrafine particles and in characterizing the chemical composition, sources, and atmospheric processing of ultrafine particles. Center investigators were among the first to use epidemiology and panel studies to demonstrate that near road exposures produce adverse health effects. They were the first to use controlled human and animal exposure studies to demonstrate that concentrated ultrafine particles cause cardiovascular effects, particularly in susceptible populations. And they have led the way using in vitro approaches to define some of the basic

cellular and molecular pathways by which ultrafine particles affect target organs differently than do fine or coarse particles. These studies will play a critical role as the EPA makes its next decision on whether to revise the form of the current PM standards.

3) Oxidative Stress

For 10 years PM investigators have been attempting to characterize the mechanisms by which PM causes adverse health effects. Increasingly, evidence is pointing to oxidative stress as a major culprit. PM Centers have been the leaders in defining reactive oxygen species (ROS) present on PM, and have shown that a variety of PM components (especially metals and organic compounds) can produce ROS in the body. They have also lead the way in demonstrating that PM can increase cellular production of ROS by interfering with mitochondrial function, and have defined the role of anti-oxidants (as well as SNPs which control anti-oxidant production) in protecting individuals from PM. These studies have changed the way in which most PM investigators view how PM affects the cardiopulmonary system. Findings that will improve understanding of whether PM components act via different pathways or a common mechanism will contribute to decisions on how best to reduce risks from PM exposure.

4) Advances in New Technology

From their initial inception, the PM Centers have been leaders in developing technology that they and other PM investigators can use. The ability to expose animals and humans to size-fractionated ambient particles is a key component of many PM research programs throughout the world. This technology was developed by PM Center investigators, who have been shared it with others. PM Center researchers have also been leaders in developing devices to monitor personal exposure to coarse and ultrafine PM, and have shared these with others who are doing panel studies to characterize the effects of these PM fractions on susceptible populations. PM Center scientists have developed technology to characterize PM components on single particles in real time and to differentially collect particles derived from different sources so they can be used in animal instillation and in vitro studies. They are developing technology to generate realistic artificial atmospheres in which the interaction of specific components and sources can be studied.

5) Health Effects of PM Sources

An important area of PM research has been a better understanding of the health effects caused by specific sources such as oil and coal fired power plants, diesel engines, or crustal material. PM Centers have played a key role in this area. They were the first to expose animals to concentrated airborne particles (CAPs) and link specific components and sources with specific biological effects in those animals. They have been leaders in showing that emissions near roadways are of special concern. The Centers and ORD scientists have collaborated on a study in which size-fractionated PM was collected from several different geographical locations (selected because each one has a different source profile) and used for animal instillation and in vitro studies, which have linked specific sources with specific biological changes.

In summary, the PM Centers have been of major importance to EPA funded PM research. Their world class scientists have focused on key problems that have significantly reduced the uncertainty about health effects associated with PM exposure and have provided important information that can be used by States and others for implementation plan development. They

have been leaders in developing key methodologies and have proposed several important hypotheses that have inspired others to take similar approaches. Their publication record is impressive and has had an impact on EPA's PM NAAQS reviews and development of policy options. Finally, the integration of the PM Centers with the ORD intramural research program has resulted in a vibrant PM research program that has been cited within EPA as a model to which other ORD programs should aspire.