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An informal one-and-a-half-day workshop devoted to research needs on the health effects of airborne particulate matter (PM) was held in Park City, Utah, on April 29 and 30, 1996, in conjunction with the Second Colloquium on Particulate Air Pollution and Health at Park City, Utah, on May 1–3, 1996. The objective of the workshop was to prepare a holistic assessment of knowledge gaps and research opportunities for presentation at the penultimate session of the colloquium. The workshop reviewed the research progress made since the first PM colloquium (Irvine, California, January 1994) and the findings of recent major reviews of the PM literature by the World Health Organization-European Region, the U.K. Health Department, the National Institute of Public Health in the Netherlands, and the U.S. Environmental Protection Agency. It then discussed: (1) the nature of ambient PM; (2) population segments at special risk; (3) the nature of the health effects of concern; (4) the sources of ambient air PM; and (5) the implications of ambient air PM health effects on occupational exposure limits and occupational cohorts. The workshop concluded that:

- A primary focus for further research should be on accumulation mode aerosol with the objective of disentangling the roles of its chemical constituents, as well as their interactive effects with each other and with coexisting gaseous criteria pollutants.
- Research is also urgently needed on the health effects of both the coarse-mode PM10 and the ultrafine particles in the nuclei-mode aerosol.
- There should be a continued focus on infants, the elderly, and people with preexisting cardiopulmonary diseases.
- Further development and validation of animal models for human sensitive groups warrants high priority.
- Validated animal models are needed for target human populations in order to investigate: (1) the roles of specific constituents of PM mixtures; (2) the roles of exposure concentrations and durations on responses; (3) some of the risk factors that predispose individuals to be responsive to PM exposures; and (4) physiological, biochemical, molecular, and pathological correlates of mortality, tissue and organ damage, and chronic disease development.

Outline of Workshop Effort

Prior to the workshop meeting, each member prepared a background document on a particular topic area, covering: (1) the current state of common knowledge; (2) conventional wisdom that warrants reconsideration; and (3) critical knowl-
edge gaps that are amenable to resolution through ongoing or new research endeavors. These individual efforts, as modified by the workshop discussions, are being submitted for publication in the colloquium proceedings. The background documents were circulated to all workshop members in advance. At the workshop, the author of each background document led an open discussion on his topic and findings. Summaries of these individual efforts, as modified by the workshop discussions, are being submitted for publication.

In preparation for the presentation of a summary report of the workshop at the colloquium and for this article, we organized our discussions as follows:

1. Progress since PM Colloquium I at Irvine, California, in January 1994. (Papers from Colloquium I were published in Inhalation Toxicology and as full proceedings.)
2. Findings of major reports on PM effects on human health by authoritative entities.
3. Framework for workshop discussions.
4. Identification of urgent research needs.

Progress Since PM Colloquium I at Irvine, California, in January 1994

We view the progress made over the last 27 months in our collective understanding of the effects of ambient air PM on human health as being remarkable in volume and content for such a relatively short interval. While the remaining unresolved issues remain quite large and formidable, we are at least at the stage of better able to formulate the critical research questions. Furthermore, there are clearly many highly competent research teams prepared to address them effectively. It is essential that coordinated efforts be made by interested parties to ensure that adequate resources and suitable funding mechanisms will be available to facilitate the necessary research.

We summarized the considerable progress made since the Irvine colloquium in terms of:

1. time-series studies of acute mortality and hospital admissions
2. cross-sectional studies of annual mortality
3. identification of PM components of concern
4. identification of thresholds
5. extent of human exposure to PM of outdoor origin

Time-Series Studies

In their summary of the mortality time-series studies at the Irvine colloquium, Pope et al. cited ten peer-reviewed studies from communities around the world. Five of these studies were based on measurements of PM concentrations of PM less than 10 μm in aerodynamic diameter (PM₁₀), and five used approximations to convert total suspended particulate matter (TSP) or coefficient of haze to PM₁₀ equivalents. They noted the consistency of the small, but generally statistically significant relative risks. Much of the open discussion at Irvine centered on the biological plausibility of the associations, and whether the associations could have been due to the nature of the assumptions made in specifying the statistical models used, or in accounting for the influence of weather on mortality. Furthermore, there was concern that most of the studies did not consider the possible influence of other pollutants in the complex ambient air mixture.

The recently released U.S. Environmental Protection Agency (EPA) PM Criteria Document (CD) cited peer-reviewed mortality studies using measured PM₁₀ concentrations from eight additional communities, including many that explicitly examined the influence of model specifications, use of various approaches to account for the influence of weather variables, and multiple pollutants. It also cited acute-mortality time-series results reported by Schwartz et al. from the Harvard six-city study in relation to measured concentrations of fine particles [i.e., PM less than 2.5 μm in aerodynamic diameter (PM₂.₅)].

Both the Schwartz et al. article and the paper presented at the Park City colloquium by Dockery et al. for a time-series analysis of daily mortality in Philadelphia during 1992 and 1993 showed that daily mortality was more closely associated with PM₂.₅ than with PM₁₀. The only exception was for Steubenville, one of the Harvard six cities, where the PM₁₀ and PM₂.₅ were highly intercorrelated.

At the Irvine colloquium, Pope et al. cited four time-series studies of hospital admissions for respiratory diseases. By contrast, the latest PM CD cited 13 such studies. The CD also cited two studies that provided the first reports of significant associations between ambient PM concentrations and hospital admissions for cardiovascular disease (CVD), which supplements prior reports about total and respiratory hospital admissions. A third report on a CVD association with PM was presented at the Park City colloquium by Fennelly and Bucher-Barelson.

Based on this greatly expanded body of time-series data, we find:

1. Prior concerns that observed PM—health associations are due largely to confounding by weather and/or to inappropriate model specification have been largely overcome. This has been done primarily through the development of reasonably well-specified and rigorous modeling approaches and the reanalysis of various data sets using alternative approaches.
2. Prior concerns about confounding by pollutant gases have been reduced.
3. The evidence for coherence among mortality and hospital admissions has been strengthened.
4. The evidence for treating fine-mode particles, as indexed by PM₂.₅, and coarse-mode particles, as indicated by PM₁₀—PM₂.₅, as separate pollutants has been strengthened.

Cross-Sectional Studies of Annual Mortality

Since the Irvine colloquium, the first longitudinal cohort study of the influence of long-term PM exposure on annual mortality by Dockery et al. has been supplemented by the American Cancer Society study of over a half-million people in 151 communities. On the basis of the consistency of the findings between these two studies that considered a wide range of individual risk factors, and with those from earlier ecological studies of annual mortality, we find that:
1. Smoking and other individual risk factors do not account for the significant associations between ambient air PM and annual mortality rates.

2. The strongest associations are with fine particle concentration (PM$_{2.5}$) and with the sulfate (SO$_{4}^{2-}$) content of PM$_{2.5}$ rather than indicators of the mass concentrations of coarser particles (TSP or PM$_{10}$).

3. The cumulative annual mortality associated with PM exposures is greater than that from excess daily mortality during peak exposures, suggesting significant life span shortening.

**Identification of PM Components of Concern**

Our continuing inability to identify specific PM constituents that may account for disproportionate portions of the health effects associated with PM exposures limits our ability to understand the nature of the underlying exposure–response relationships. It also impedes the initiation of efficient control strategies.

The increasing concern about fine particles evident since the Irvine colloquium has stimulated greater interest in some specific chemical components of the accumulation mode aerosol, as well as of the more transient ultrafine particles in the nuclei mode. The ultrafine particles contribute little mass to the fine fraction. However, they dominate the particle surface area and the particle number concentration. The potential importance of particles with diameters of ~20 nm is illustrated by the evidence for adverse effects from studies by Oberdörster et al.\(^{(15)}\) with very low mass concentrations of insoluble ultrafine particles and by Chen et al.\(^{(16)}\) with very low H$^+$ concentrations on ultrafine particle surfaces. We need to know more about how insoluble ultrafine particles rapidly penetrate the respiratory epithelium and how acidic ultrafine particles stimulate mediator release from respiratory epithelial cells.

From among the numerous chemical constituents of the accumulation mode PM, our discussions focused on the strong acid component of the aerosol (H$^+$), SO$_{4}^{2-}$, the transition metals that stimulate reactive oxygen species (i.e., iron, vanadium, nickel, copper, and zinc), organics, and allergens, as well as on potential synergistic interactions among these constituents.

H$^+$ remains a viable candidate for a disproportionate share of the effects produced in populations by the fine particles on the basis that: (1) it is the only constituent that has produced physiological and toxicological responses in controlled short-term exposure studies at near-ambient concentrations that are consistent with effects seen in population studies; and (2) it has been found to be the single PM index most closely associated with excess hospital admissions for respiratory diseases in Toronto\(^{(17)}\) and with respiratory and CVD mortality and hospital admissions in Buffalo, New York.\(^{(18)}\) On the other hand, in several other epidemiologic studies in which H$^+$ was measured, it has not been measured at generally detectable levels or found to be as highly correlated with the responses as fine particle mass or sulfate.\(^{(6,19)}\)

SO$_{4}^{2-}$ has been as closely, or often more closely, associated with human mortality and morbidity indices than other PM metrics.\(^{(20)}\) This could be due to its relatively small measurement error, its utility as a conservative metric of exposure to PM of outdoor origin both indoors and outdoors, its close association with H$^+$, or its being closely associated with other reactive chemical species in the atmosphere. For example, at the Park City colloquium, Friedlander and Yeh\(^{(21)}\) demonstrated that SO$_{4}^{2-}$ was closely associated with peroxides in ambient air, and that peroxides were plausible candidates for causal chemical species in relation to human health effects.

Transition metals in soluble forms are released to the atmosphere from combustion sources as ultrafine particles, and can build up in the atmosphere on accumulation mode particles. Recent research presented at the Park City colloquium by Ghio et al.\(^{(22)}\) and Dreher et al.\(^{(23)}\) has demonstrated that these metal ions, when administered via intratracheal instillation, can generate reactive oxygen species in the lungs that could account for many of the adverse cardiopulmonary health effects of concern. However, there have not yet been any reports demonstrating that such effects can be produced via inhalation at PM concentrations near those measured in the ambient air.

On the other hand, long-term exposure to low concentrations of carcinogenic trace metals could be related to the suggestive evidence from the chronic mortality epidemiology for PM-associated elevations in cancer risk reported by Dockery et al.\(^{(12)}\)

Trace organics in PM could also play a role in the suggestion of excess cancer risks associated with long-term PM exposure. Also, to the extent that organics within thoracic PM stimulate the generation of reactive oxygen species, they may possibly also play a role in the cardiopulmonary effects associated with PM exposures.

Airborne allergens are a well-established class of causal agents for cardiopulmonary health effects, with strong seasonal influences. However, most of the aeroallergens found outdoors are of natural origin and are not amenable to control by regulatory agencies. Airborne allergens of indoor origin, such as those from dust mites, animal dander, roaches, molds, mildew, and fungi, can also be important confounding cardiopulmonary stressors not amenable to control by governmental agencies. In any case, research is needed to better determine the interactive effects of exposures to abiotic anthropogenic air pollutants and aeroallergens.

There is an urgent need for studies of the effects of the kinds of complex mixtures typically present in regional and urban airsheds. The papers presented at the Park City colloquium by Godleski et al.\(^{(24)}\) on excess mortality in hypertensive and bronchitic rats exposed to concentrated Boston winter accumulation mode aerosol, and by Kleinman et al.\(^{(25)}\) on enhanced cellular and physiological effects in aged rats exposed to laboratory-generated mixtures of mineral dust, acidic aerosol, and ozone provide strong evidence that laboratory studies of realistic complex PM–gas mixtures can produce biological effects comparable to those reported in human populations at much lower concentrations than those required for the gaseous pollutants within the mixtures. As these types of studies more clearly establish the nature and extent of the effects that can be produced by complex PM–gas mixtures, it may be possible to disentangle the roles of one or more of the specific components within the mixture by selective removal or neutralization of components and/or by selective enhancement of the concentration ratios of some of the more potent components.

In summary, we now appear to be on the threshold of rapid expansion of our knowledge of underlying biological mecha-
nisms that can account for the kinds of cardiopulmonary effects associated with population exposures to PM in ambient air. We now have more testable hypotheses as well as new technologies for generating more relevant test atmospheres for controlled exposure studies. These advances, when combined with the recently developed tools of molecular biology, analytic biochemistry, pathological analyses, and functional assessment, provide the sensitive means needed for effective testing of our more sophisticated hypotheses.

**Evidence for Thresholds**

The search for evidence of effective thresholds in large population studies of air pollution health effects continues. There are inherent limitations associated with measurement errors in both the exposure and the effects estimates. There are also limitations imposed by a broad range of sensitivities associated with constitutional factors and other environmental and disease factors that vary across human populations. The Park City colloquium paper by Cifuentes and Lave(26) was interpreted to suggest different effective thresholds in Philadelphia and Santiago, Chile, but not in Birmingham, Alabama. Various other authors have explored for thresholds using quintile or quartile analysis of PM levels or by estimating the exposure–response relationship with nonparametric smooths of PM, controlling for other factors. Such approaches have been used for many areas (including Philadelphia). Overall there is not yet consistent evidence available for a threshold, and the majority of the studies suggest a monotonic, near-linear exposure–response relationship.

**Exposure to PM of Outdoor Origin**

There has been important progress since the Irvine colloquium in our understanding of the relationships between central station pollutant concentrations data and population distributions of exposures.

It has long been known that the fine- and coarse-mode components of the ambient aerosol have distinctly different sources and chemical compositions, and that reductions in human exposures to fine particles will necessitate quite different kinds of emission controls than those developed for and traditionally applied to coarse particle control. What is new in recent years is a body of data on the extent of penetration of PM of outdoor origin into indoor environments and their persistence indoors after their penetration. All thoracic particles (PM$_{10}$) of outdoor origin can infiltrate indoors with high efficiency. The nonreactive fine particles persist in the indoor air for many hours. Once indoors, reactive fine particle components, such as H$^+$, are gradually neutralized by ammonia from indoor sources. The coarse component of PM$_{10}$ decays rapidly, once indoors, by sedimentation. Reactive pollutant vapors, such as ozone and sulfur dioxide rapidly decay by reactions with interior surfaces.

Indoor fine particle mass concentrations are generally poor surrogates for exposures to fine particles of outdoor origin because of the influence of fine particles of indoor origin (e.g., from smoking or cooking). On the other hand, SO$_4^{2-}$, being present as nonreactive fine particles, formed in the atmosphere on a regional scale, can serve as an excellent tracer for fine PM of outdoor origin.$^{5,20}$

By contrast, the mass concentration of PM$_{10}$, with widely varying ratios of coarse to fine mass in terms of region, local area, and time, is highly dependent on the presence of local sources of coarse particles and wind patterns. As a result, there can be much greater variations from one monitoring site within a community to another in PM$_{10}$ mass concentration than in fine particle mass concentration. Thus, if PM$_{10}$ monitoring data are to be used for epidemiological studies, then multiple monitoring site averages will provide much more reliable estimates of population exposure to PM$_{10}$ than any single site’s data, except in situations where an extended set of local calibration studies have demonstrated that a single site can provide a good representation for the larger community. For coarse PM, indoor sources, such as dust resuspension from furniture and floors, can dominate personal PM$_{10}$ exposures.

It has also become clear in recent years that there are important unresolved technical issues in the measurement of the mass concentrations of ambient air PM$_{10}$. We have learned that the semivolatile components—especially ammonium nitrate, but also wood smoke and some organic components of photochemical smog—are not fully retained on sampling filters. In the western United States, where nitrates and organics can constitute large fractions of PM$_{10}$, network monitoring data can significantly underestimate actual PM$_{10}$ exposures.$^{27}$

The problem is even more severe for fine fraction of PM$_{10}$, since essentially all of the semivolatile PM$_{10}$ is contained within the fine fraction. Also, the problem may be more severe for PM monitors with heated inlets than for manual samplers.

In the eastern United States, where there are much lower concentrations of ammonium nitrate and much larger concentrations of acidic sulfates, there can be another, quite different systematic error in reported PM$_{10}$ concentrations. This is because the acidic sulfates are strongly hygroscopic and take up water vapor when ambient humidities are elevated, as is typical during the summer in the humid eastern United States. Some of the retained water remains on the filter even after equilibration to standard conditions in the analytic laboratory. As documented in the latest EPA PM CD,$^{5}$ a large fraction of the reported PM$_{10}$ mass in the eastern United States cannot be accounted for by chemical analyses of sampling filters and presumably is particle-bound water. Under such conditions, reported PM$_{10}$ concentrations in the east overestimate true ambient PM exposures. Since almost all of the sulfate is in the fine fraction, this problem is also more severe for the fine fraction than for PM$_{10}$ as a whole.

The selection of an optimal cut size for the aerodynamic separation of the fine and coarse fractions of PM$_{10}$ is complicated by the different humidity ranges in the east and west, as well as by the different proportions of fine and coarse particles. In the arid west, essentially all of the fine-mode particles are below 1 $\mu$m in diameter, and strong winds can produce a coarse-mode distribution tail with a significant mass in the 1- to 2.5-$\mu$m range. Thus, a 1-$\mu$m cut size might be ideal for arid areas of the western United States. By contrast, in the humid eastern United States, a significant portion of the hygroscopic sulfate aerosol can be found in the size interval between 1 and 2.5 $\mu$m, and coarse-mode intrusion into this size interval is generally low. Thus, for the eastern United States, an aerodynamic cut size at 2.5 $\mu$m diameter is preferable.

Since it is unreasonable to expect that future PM standards will accommodate regional variations in cut size, accommo-
Major Reports on PM Effects on Human Health

In the interval between the Irvine and Park City colloquia, four authoritative entities have drawn conclusions about the health impacts of ambient air PM.

The World Health Organization-European Region (WHO-EURO) has prepared revised Air Quality Guidelines for a variety of air pollutants, including PM. Its earlier guidelines were based on the premise that there were no observable adverse effects levels (NOAELs) and that public health could be protected by establishing a lower concentration limit than the NOAEL using a safety factor. The latest WHO-EURO expert committee for PM concluded that there was no current basis for establishing a NOAEL for PM. It recommended instead that the exposure–response relationships for PM10 and PM2.5, as interpreted and tabulated by the expert panel, be reported with tabular guidance and interpretive text for use by national authorities in establishing their own air quality standards. Thus, the burden is on the national authorities to determine their own acceptance limits for the public health impacts of exposures to ambient PM.

A second authoritative report from the U.K. Department of Health concluded, with typical British understatement, that, “In terms of protecting public health it would be imprudent not to regard the demonstrated associations between daily concentrations of particles and acute effects on health as causal.”

A third report, the 1993 Revision of the PM CD issued by the National Institute of Public Health in the Netherlands, concluded that:

- Our current understanding of the toxicology of ambient PM suggests that fine and coarse particles may have different biological effects.
- The evidence for PM-related effects from epidemiologic studies is fairly strong, with most studies showing increases in mortality, hospital admissions, respiratory symptoms, and pulmonary function decrements associated with several PM indices. These epidemiologic findings cannot be wholly attributed to inappropriate or incorrect statistical methods, misspecification of concentration–effect models, biases in study design or implementation, measurement errors in health endpoint, pollution exposure other than PM, weather, or other variables, nor confounding of PM effects with effects of other factors.
- Within the overall PM complex, the indices that have been most consistently associated with health endpoints are fine particles, thoracic particles (PM10 or PM15), and sulfate (SO4{2-}). Less consistent relationships have been observed for TSP, strong acidity (H+), and coarse PM (PM10–PM2.5).
- There is evidence that older adults with cardiopulmonary disease are more likely to be impacted by PM-related health effects (including mortality) than are healthy young adults. The likelihood of ambient fine-mode particles being significant contributors to PM-related mortality and morbidity among this elderly population is bolstered by: (1) the more uniform distribution of fine particles across urban areas and their well-correlated variation from site to site within a given city; (2) the penetration of ambient particles to indoor environments (where many chronically ill elderly individuals can be expected to spend most of their time); and (3) the longer residence time of ambient fine particles in indoor air, enhancing the probability of indoor exposure to ambient fine particles more so than for indoor exposure to ambient coarse particles.

Framework for Workshop Discussions

Upon completion of our reviews and discussions of the background documents prepared by each member of the workshop panel, we continued our discussions along broader, more integrated themes. These were:

1. The nature of ambient PM as it relates to human health effects.
2. Population segments at special risk.
3. The nature of the effects of concern.
4. The sources of PM with special reference to control strategies.
5. The implications of current knowledge of the health effects of ambient PM of outdoor origin on occupational exposure limits and occupational cohorts.

With regard to the nature of ambient PM in relation to human health effects, we concluded that:

- A primary focus for further research should be on accumulation mode aerosol with the objective of disentangling the roles of its chemical constituents, as well as their interactive effects with each other and with coexisting gaseous criteria pollutants.

The focus is warranted because the best established PM-associated human health effects are most closely associated with...
the concentrations of fine particle mass, sulfate, and hydrogen ion. Other accumulation mode constituents warranting further investigation are the transition metals and organics on the basis of their demonstrated biological effects in laboratory assays and their potential carcinogenic effects.

- Research is also urgently needed on the health effects of both the coarse-mode PM$_{10}$ and the ultrafine particles in the nuclei-mode aerosol.

While epidemiological evidence for coarse-mode PM$_{10}$ (i.e., PM$_{10}$-PM$_{2.5}$) is, at best, only suggestive, it is likely that at least some of the effects associated with PM$_{10}$, such as excess bronchitis incidence and exacerbation of asthma, were due more to coarse-mode PM$_{10}$ than to the PM$_{2.5}$ fraction. It is well known that occupational exposure to mineral dusts causes industrial bronchitis, and that dust and fog exposures can exacerbate asthma.

Heyder et al.,$^{(52)}$ at the Park City colloquium, provided a report of the first study linking human responses to PM more closely to the number concentration than to the mass concentration of fine particles. This, plus the more speculative evidence from animal inhalation studies with high number concentrations (but low mass concentration) of insoluble ultrafine particles$^{(15)}$ and of acidic ultrafine particles,$^{(16)}$ demonstrates the need for more intensive epidemiological and controlled exposure studies of the health effects of ultrafine aerosols.

As for the populations of special concern with regard to the human health effects of exposures to PM of outdoor origin, we concluded that:

- Continued focus on infants, the elderly, and people with preexisting cardiovascular and pulmonary diseases is warranted in further epidemiological studies, especially in studies relating quantitative determinations of individual exposures in relation to morbidity endpoints.
- Further development and validation of animal models for human sensitive groups warrants high priority.
- The availability of validated animal models for at least some, if not all, of the human populations likely to be most susceptible to health effects associated with ambient air PM exposures will make it possible to investigate a number of important factors, such as: (1) the roles of specific constituents of PM mixtures; (2) the roles of exposure concentrations and durations on responses; (3) some of the risk factors that predispose individuals to be responsive to PM exposures; and (4) physiological, biochemical, molecular, and pathological correlates of mortality, tissue and organ damage, and chronic disease development.

With regard to effects of concern, emphasis should continue to focus on effects reported in the epidemiological studies and their correlation in animal models of susceptible populations. These effects include:

- sudden death
- reduced longevity
- admission to emergency room and hospital
- lost time (from school or work)
- supplemental medication usage
- increased rate of infections
- increased symptom rates
- reduced lung function

With regard to PM sources and their implications for control strategies, we note that the prior NAAQS, based on TSP, and the current NAAQS, based on PM$_{10}$, being mass concentration limits, drive control strategies toward an emphasis on limiting emissions of primary particles. Since primary particles are largely coarse particles, there has been relatively less attention paid to controlling gas phase precursors of fine particles. Also, state and local control agencies recognize that emission controls on gaseous precursors of fine particles will have little impact on PM$_{2.5}$ concentrations within their own jurisdiction and cannot influence the ambient PM$_{2.5}$ concentrations attributable to source emissions in upwind regions. It follows that future control programs for PM$_{2.5}$ can only be fully effective if they are based on regional rather than local control strategies.

With regard to the implications of our increased understanding of the health effects of ambient air PM of outdoor origin on workers with chronic exposures to dusts and vapors, our primary concern focused on the prospects that such workers are likely to constitute a susceptible subpopulation. It is well established that long-term exposure to mineral dusts can lead to chronic bronchitis and accelerated loss of lung function, and that these conditions can progress even after the occupational exposures end. Miners and other workers in dusty trades may retire with lung function in the normal or near-normal range and then become progressively disabled. This is because of dust that accumulates around small airways, and the loss of lung recoil, which is a normal part of lung aging, results in airflow obstruction. They would become a sensitive population group in terms of pneumonia or if CVD is added to an existing burden. Registries of such workers, if enrolled in prospective cohort studies, may be ideal populations for further studies of both acute and chronic air pollution mortality and morbidity.

In designing future studies of the health effects of occupational exposures to PM or to mixtures of PM and irritant vapors, consideration should be given to the hypotheses generated by the recent epidemiological research on ambient air PM. Attention should be paid to cardiovascular and respiratory symptoms and functions in occupationally exposed workers, as well as to daily variations in their responses that may be related to variations in their exposures to environmental pollutants.

**Urgent Research Needs**
For the purpose of this article, our research recommendations are summarized in terms of:

1. particle composition and size
2. studies of human populations
3. animal models for toxicological studies
4. exposure assessment

**Particle Composition and Size**
There is a critical need to identify the components and size characteristics of ambient PM that contribute to the adverse responses demonstrated in epidemiology studies. Understanding which components or interactions between components are essential to the toxicity of PM will be useful in designing appropriate monitoring and potential control strategies. A more detailed discussion of data gaps and research needs in this
area was presented at the Park City colloquium by Driscoll and Jarabek. Some urgent research areas include:

- Definition of interactions between PM components. Most studies have focused on exposures to only one or two components of ambient PM. There is increasing evidence that interactions occur between components of ambient PM as well as between PM and gaseous pollutants, and that such interactions result in increased toxicity. Better definition of interactions between PM components is needed, as are studies on whole (concentrated) ambient PM. Since chemical reactions between materials on the surfaces of particles may account for the synergistic effects of PM components, a better understanding of this chemistry, as it relates to the formation of more toxic materials as well as the interactions between particle surfaces and host factors (cells, proteins, lipids) within the lung, is needed.

- Identification of critical targets of PM effects. Cytotoxicity, inflammation, oxidant stress, and altered lung cell function have all been reported as aspects of the respiratory tract response to relatively high concentrations of ambient PM components. Defining the critical in vivo targets (e.g., epithelial cells, macrophages, upper or lower airways, etc.) and the nature of the effects (e.g., oxidant production, cytokine release) within and outside the respiratory tract will be key to developing more sensitive approaches and biomarkers to assess the adverse effects of PM in toxicology and clinical studies.

- Toxicity of ultrafine particles. Studies on ultrafine particles indicate that they can be highly toxic in the lung, particularly when exposure is to large numbers of single-particle exposures. Studies are needed to further define environmental exposure to ultrafine particles, as well as the nature of these particles, to better appreciate the relevance of recent laboratory findings. Additionally, a better understanding of the mechanisms underlying the toxicity of ultrafine particles is needed.

- Dosimetry. In considering exposure–response relationships for particles, at present, it is not clear which dose metric (e.g., mass, surface area, particle number) is most appropriate for assessing fine-particle exposure as it relates to potential toxicity. Additional studies characterizing relationships between particle surface, number, and mass and responses to exposures to ambient PM and its components are needed.

- Interactions. The fine-particle component of ambient PM provides a large surface area onto which materials may become adsorbed (vapors, gases) and react, resulting in the formation of toxic materials such as reactive oxygen species. Additionally, fine particles may act as vehicles to deliver surface adsorbed materials to sites in the lung they would not otherwise reach in significant concentration. The extent to which fine particles act to promote reactions between components of ambient pollution and deliver the products to the deep lung needs to be investigated. This information could provide insights into potential mechanisms of toxicity, as well as guide development of better approaches for generating test aerosols that most closely mimic ambient PM.

**Studies of Human Populations**

Current epidemiologic evidence suggests that thoracic particulate air pollution, at levels common to many urban and industrial areas in the United States, contributes to human morbidity and mortality. Long-term, repeated exposure increases the risk of chronic respiratory disease and the risk of cardiorespiratory morality. Short-term exposures can exacerbate existing cardiovascular and pulmonary disease and increase the number of persons in a population who become symptomatic, require medical attention, or die. The pattern of cardiopulmonary health effects associated with particulate air pollution that has been observed by epidemiological studies is currently the strongest evidence of the health effects of this class of pollutants. Nevertheless, the epidemiological studies have important limitations that stem largely from the use of people who are living in uncontrolled environments and who are exposed to complex mixtures of particulate air pollution.

In addition to providing limited information about biological mechanisms, current epidemiological studies provide relatively meager information regarding linkages between ambient and personal exposures, and are unable to fully explore the relative health impacts of various constituents of air pollution. Future research needs to integrate epidemiological studies and exposure assessment studies. Efforts to understand relationships among different ambient air pollutants, as monitored at central monitoring sites, and their relationships to personal exposures need to be considered in studies of associations of exposures with cardiorespiratory health endpoints. Such an approach can be used with cohort- or panel-based time-series or cross-sectional studies. Ideally, structurally linked multi-area studies would be used to help disentangle independent effects or potential interactions among risk factors that exist and are highly correlated in some areas but not in others.

Future research needs to help provide a better understanding of the relative importance of chronic and acute exposures. Much of the recent epidemiological effort has focused on effects of acute exposure, primarily because of the relative availability of relevant time-series data sets. However, the effects of chronic exposure may be more important in terms of overall public health relevance. Such research is also needed to provide a better understanding of susceptible populations. For example, individuals susceptible to serious effects of acute exposure may only be those with existing respiratory and/or cardiovascular disease, but a much larger segment of the population may eventually be seriously affected by chronic, long-term exposure.

**Animal Models for Toxicological Studies**

The paucity of toxicity data on ambient PM is due to the lack of validated and relevant laboratory animal models having the characteristics of compromised human subjects. The validation of such animal models will be very useful and illuminating in explaining the epidemiological findings. Animal models that have been developed for human pulmonary and cardiovascular diseases include respiratory allergy (asthma), chronic bronchitis, pulmonary emphysema, aging, pulmonary hypertension, congestive heart failure, and respiratory infection. Such models were described in detail at the Park City colloquium by Cassee and Van Bree, but it will be necessary to further develop and validate these models. Important questions with respect to such models are: (1) How do they reflect the pathological features of human diseases, and what parameters should be used to measure these effects? (2) Can we control the severity of the
In compromised animals, and what is the stability and the reproducibility of a model? Moreover, most of the available models can only be used for acute and subacute toxicity studies, but there is an urgent need for models that can be used in chronic or subchronic toxicity studies. Some of these questions can only be properly addressed when we know more about which human populations are experiencing the various kinds of effects and what kinds of exposures are associated with these effects.

**Exposure Assessment**

Improvements are needed in all of the PM measurement methods, especially in terms of methods that provide continuous analyses of ambient concentrations and/or integral analyses over extended time intervals. Such methods can provide better data for both exposure and compliance analyses and may also, at the same time, reduce monitoring costs in relation to daily manual sampling and analyses of PM filters. These needs were described in detail at the Park City colloquium by Wilson. The data generated by these improved measurement methods can also be used for systematic studies of exposure misclassification and measurement error. Such studies can provide an improved basis for the analysis of population distributions of exposures in epidemiological studies, and for analyses of population distributions of exceedances of ambient air quality standards for risk analyses.

Other important exposure-related PM research needs include:

- Accumulation of more comprehensive information on the particle size distribution of ambient PM in representative cities in different parts of the United States having different source types. A comparison of particle size distributions by count and mass is especially important.
- Determinations of which species and size of PM components are sufficiently evenly distributed across large urban areas to be suitable for epidemiological studies.
- Development of appropriate exposure assessment protocols for epidemiological studies that test specific hypotheses.
- Enhancement of the database on infiltration ratios (ambient into microenvironments) and activity patterns (time in various microenvironments) to improve exposure assessments for epidemiological studies.
- Development of improved methods for measuring the concentrations of biological particles, including endotoxins, pollens, spores, and insect debris in morbidity studies.
- Characterization of size, composition, and concentration of concentrated ambient particles in laboratory exposure studies, including measurements of coexisting gaseous pollutants and toxic gases dissolved in particle-bound water.
- Development of better understandings of ambient/indoor/personal exposure relationships, their significance for various epidemiological studies, and how they can be used to improve assessment of exposure to ambient PM.

In addition, better integration/coordination of compliance and epidemiological monitoring is needed. Finally, in developing a federal reference method, it is important to specify precise methods suitable for determination of trends and of compliance with PM mass standards without limiting improvements in measurement technology for continuous or long-term monitors or for techniques that measure all components of PM mass.

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**References**