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### Permalink

<https://escholarship.org/uc/item/4pp0136z>

### Journal

Applied Occupational and Environmental Hygiene, 13(6)

### ISSN

1047-322X

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### Publication Date

1998

### DOI

10.1080/1047322X.1998.10389558

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Peer reviewed

# Research Needs Relating to Health Effects of Exposure to Low Levels of Airborne Particulate Matter

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Concern over the consistent and reproducible epidemiological associations between particulate air pollution and human mortality and morbidity stimulated a series of two international scientific colloquia. The first was held January 24–25, 1994, in Irvine, California, and the second was held May 1–3, 1996, in Park City, Utah. Each colloquium was attended by about 200 epidemiologists, toxicologists, chemists, clinicians, regulators, and other concerned specialists. At both colloquia, attendees were asked to submit written suggestions for future related research after they had listened to numerous formal papers and after participating in several open discussions. It is important to note that these research suggestions represent snapshots in time of the ideas of a large group of well-informed experts with varied backgrounds; these recommendations do not carry the imprimatur of the colloquium sponsors, any regulatory body, or any other agency. This article summarizes the research suggestions from the second colloquium; a similar article was published relating to the earlier colloquium.<sup>(1)</sup>

The suggestions from attendees of the second colloquium, over 160 in total, were first sorted into broad categories based on the type of project suggested (epidemiology, toxicology, sampling, etc.), and then similar studies were combined under a single description. Some projects were suggested by five or more individuals, most by two or three individuals, and about 25 percent by only one person. In the summary lists that follow, the projects listed first within each category are those that were most frequently suggested.

## Research Needs by Category (Projects Are Not Necessarily Mutually Exclusive)

### *Studies Related to Air Pollution Epidemiology and Epidemiologic Methods*

1. Longitudinal panel studies of morbidity and mortality in healthy and compromised individuals (bronchitis, cardiovascular-compromised, etc.), with personal exposure characterizations.
2. Effects of long-term exposures with extensive data collection, including personal exposures and weather parameters.
3. Studies of the effects of exposure assessment errors on epidemiology study findings.
4. Meta-analyses in which studies are combined in order to identify roles of specific exposure agents.
5. Studies in cities (including those in Eastern and Western

Europe) which have high and low extreme levels of pollutants. Complete monitoring data are required.

6. Investigations of the effects (roles) of personal exposures on epidemiologic findings.
7. Collaborative (between economists and epidemiologists) research focusing on cost-benefit analyses and health valuations.
8. Comparisons of mortality rates and incidence of diseases for the following: clean and highly polluted days; clean and highly polluted cities; and cities that have improving air quality.
9. Health effects of personal exposures, including studies of hospital deaths (with thorough monitoring of chemical species).
10. Incorporation of autopsy data into epidemiologic investigations.
11. Investigations directed at threshold phenomena.
12. Studies to explain the observed increases in asthma rates in light of improving outdoor air quality.
13. Investigation of population characteristics (as opposed to individual characteristics) in relation to morbidity and mortality.
14. Additional investigations of the roles of nonparticulate pollutants in epidemiologic investigations of particulate matter.

### *Occupational Cohort Studies*

1. Follow-up of particle-exposed occupational cohorts after retirement to look for chronic illnesses and possible induced sensitivity to environmental particulate air pollutants.
2. Studies of cohorts with current heavy particle exposures to look for excess cardiopulmonary-related morbidity and mortality.

### *Clinical Studies*

1. Investigations of pollutant deposition and clearance in subjects with existing pulmonary diseases.
2. Investigations of pollutant effects in subpopulations that are expected to have enhanced sensitivity to particulate air pollutants.
3. Investigations of ventilatory and activity patterns for various types of people.
4. Investigations relating to the possibility of differentiating particulate-caused cardiovascular (and pulmonary) deaths from deaths produced by other causes.

### *Toxicology Studies*

1. Mechanism of action studies (hypothesis driven) that include cardiac as well as pulmonary effects.
2. Investigations of the roles of specific chemical constituents of air pollution, including transition metals, hydrogen ions, reactive chemical intermediates, and semivolatile species.
3. Studies of the roles of particulate mass, particulate surface area, and particulate number in relation to biological effects.
4. Development of new animal models that mimic human diseases, or that are more sensitive than existing models.
5. Investigations of ultrafine particles: their deposition, translocation, clearance, and effects. (Note that no single accepted definition of ultrafine exists, but this context implies particles with diameters under 0.1  $\mu\text{m}$ .)
6. Studies that investigate medical plausibility hypotheses which can be related to adverse human health effects.
7. Particle deposition and clearance studies in healthy and diseased animal models.
8. Exposures to actual ambient pollutants, or otherwise more realistic physical and chemical forms of ambient pollutants.
9. Studies of combinations of pollutants (including thermal stress as a cofactor) that contain both particles and gases.
10. Dose-response and threshold studies in animal models that represent sensitive human subpopulations.
11. Studies of interactions of particulate material and oxygen radicals.
12. Long-term studies, including those that relate acute effects to chronic effects.
13. Studies of sensitization to ambient air pollutants.
14. Additional toxicology studies on indoor-source pollutants.
15. Studies of the toxicologic effects of coarse particles. (Note that in this context, coarse particles have aerodynamic diameters larger than 2.5  $\mu\text{m}$ .)
16. *In vitro* exposures of respiratory tract cells to realistic particles.

### *Sampling, Analysis, and Exposure Assessment Investigations*

1. Improvements in equipment and procedures used for monitoring particle size and composition, including ultrafine particles and semivolatile components (especially using denuder-related technology). Also, monitors that are smaller, less expensive, and lighter are needed for PM<sub>10</sub> and PM<sub>2.5</sub> measurements in the field.
2. Gathering of additional data on particulate matter size distributions and chemical compositions.
3. Studies that correlate indoor and outdoor particulate levels, and that better define personal exposures.
4. Development of continuous (or short averaging time) monitors for PM<sub>10</sub> and PM<sub>2.5</sub>.
5. Studies of source apportionment and studies leading to improvements in modeling the effects on air pollution of changes in source strengths.
6. Characterizations of indoor exposures, and definition of the inhaled doses to people from indoor air pollutants.
7. Studies of interactions among realistic combinations of air pollutants, including particles and gases (both short-lived and long-lived).

8. Improved personal exposure characterizations.
9. Interactions of viable and nonviable pollutants, including those that are infectious and allergenic.

### *Dosimetry-Related Investigations*

1. Development of improved dosimetry models that apply to individuals, rather than simply to an average adult.
2. Basic airway anatomical data that relate to modeling the deposition and fates of particulate and gaseous air pollutants.
3. Improvements in techniques used for assessing potential risks, including more holistic approaches that balance risks from various causes.

### *Practical Considerations*

It was clear from some of the written comments that the needed research could not be performed without first solving some practical problems. These practical considerations included the following:

1. A central repository for data, including epidemiologic, toxicologic, and atmospheric, is needed so that new studies can be better designed, interpreted, and integrated. Also, such a repository would facilitate meta-analyses and prevent unnecessary duplication.
2. International cooperation should be encouraged, as it is required for fostering progress on many aspects of the problem of particulate pollution and human health.
3. Additional funding should be made available for the needed research. This will require the cooperation of local, federal, and international governments; businesses; and other private agencies.
4. A perpetual Colloquium on Particulate Matter and Human Health, with permanent staff and a World-Wide Web page, should be seriously considered. A 2-year interval between meetings was the most common recommendation.
5. A two-tiered air monitoring system is needed, in which cities involved in epidemiologic studies have more complete, research-quality monitoring. Other cities not involved in studies would presumably have less expensive monitoring stations that are geared toward evaluating compliance with existing air pollution regulations.
6. A complete bibliography on all aspects of particulate matter and health should be established and maintained current.
7. The Environmental Protection Agency's deposition modeling program should continue, and it should have adequate support.

### *Major Unresolved Issues*

Few, if any, informed people are likely to doubt the validity of the epidemiologic associations between ambient particulate mass sampling and data on human mortality and morbidity. However, the reasons for this association are currently undergoing intense scientific scrutiny and debate. Experts also disagree on whether or not sufficient evidence against particle mass exists to support intensified mass-based controls. What is at stake is great, because a premature judgment that leads to ineffective, costly controls could have a burdensome impact that could seriously wound the trust that the public has in the regulatory and scientific communities. Therefore, it is impor-

tant to carefully examine all significant issues that are not well understood.

From looking at the preceding lists of research needs, some larger uncertainties can be seen—some clearly, and some less distinctly. These uncertainties include the following:

### *Who? What? and How?*

Assuming the excess mortality is real, it is clear that we cannot confidently answer the following three questions: Who is dying? What agents are killing them? and How are the causal agents acting? It can be argued that in order to implement regulations that effectively decrease the risk, more specific information is needed than simply an epidemiological association. It is important to know who is dying. For example, is it only critically compromised persons in some specific indoor locations, such as hospitals, or are the victims virtually everyone exposed anywhere in a polluted city? Similarly, what is causing the deaths? Is it the number of sub-tenth micrometer diameter insoluble particles inhaled over the period of a day? Is it some unique combination, such as an acid-coated particle that contains transition metals? Or is it everything together (all air pollutants) acting as a lethal soup? The answers to these questions could be important in devising efficient and effective control strategies. Also, what is the mechanism of death? Is it upper airway inflammation? Is it alveolar inflammation and interstitial edema? Is it all of the above, plus other causes? Again, intervention strategies could be best designed if these questions can be clearly answered. Many, if not all, of the previously identified research needs are related in one way or another to one or more of these questions.

### *Medical Plausibility*

Substantial differences of opinion exist regarding the necessity of establishing a link between particulate exposure and death or injury. What is meant by "medical plausibility"? At one extreme, it is something similar to a proof in geometry. Given some solid basic assumptions about physics, chemistry, and physiology, one might establish an unbroken chain of events (such as pollutant deposition, early response, secondary reactions, organ failure, etc.), at the end of which death or debility is virtually certain. Such logical proofs do exist for many illnesses and poisonings, and when this is the case, intervention (at least in principle) is straightforward. At the other extreme, "plausibility" might simply mean that there is an absence of proof of absurdity. Intense smog episodes kill people, so why not smaller ones? A substantial fraction of the previously listed research needs, especially those in the toxicology category, relate to the plausibility question.

### *Defining Particulate Matter*

On the face of it, particulate matter seems to be a relatively unambiguous entity: it is just the condensed matter in the air. But two substantial problems exist with this simple definition. First, one can measure particulate matter by total count, total surface area, total mass, nonaqueous mass, insoluble mass, nonbiogenic mass, etc. Which is the relevant measure, or which are the relevant measures, for the presumed adverse health effects? Second, the condensed particulate phase is very dynamic; volatiles evaporate and condense; chemical reactions change the composition and mass; the surrounding conditions,

including temperature, humidity, and gaseous compound concentrations, also can rapidly change the particulate composition and mass. Is the mass and composition on a filter (at laboratory conditions) the relevant particulate matter, or is the airborne, condensed phase as it exists just outside of the human nose (or inside the trachea) most relevant? Several items in the suggested research list, especially in the sampling, analysis, and exposure assessment category, relate to this large issue.

### *Effects of Control Strategies*

Any control strategy will have several effects; some will be reasonably predictable, and some may not be so predictable. A tightened standard, for example, will possibly produce adjustments in industrial processes, changes in the costs of products, changes in illness patterns, and new atmospheric chemistry processes. What will be the net consequences of all of these changes? The suggested research projects (especially in the epidemiology section) include items that address this important question.

### *Occupational Implications*

Historically, the protection of workers from adverse effects has followed strategies that differ substantially from those used in environmental exposure situations. Specifically, the focus is on individual, rather than mixed, pollutants, and on small, highly exposed, relatively healthy populations. What can be learned from the occupational health literature that helps us to understand environmental exposures, and vice versa?

### *Levels Versus Increments*

Much (but not all) of the recent epidemiological research is based not on average air pollutant particulate levels, but on changes (or increments) in the level; the larger the incremental increase in particulate matter, the larger the associated health effects. Does this imply that any level of particulate pollutant, even one as low as a few tens of micrograms, is associated with adverse effects? Research suggestions that involve thresholds, dose-response considerations, and effects of cleaning the air address this issue.

### *What Is the Proper Metric for Compliance?*

This question is clearly related to the section on defining particulate matter; and several other suggested research projects directly apply to this question as well. On one hand, because the epidemiologic associations are based on PM<sub>10</sub> and PM<sub>2.5</sub>, such measures (metrics) seem to be acceptable ones with which to evaluate community compliance with regulations. On the other hand, if such measures are surrogates for the actual culprit(s), it can be argued that community compliance with regulations that are based on PM<sub>10</sub> and PM<sub>2.5</sub> might not guarantee that adverse health effects are adequately controlled.

### *Summary and Conclusions*

Attendees of the Second Colloquium on Particulate Air Pollution and Health offered over 160 suggestions related to needed research. These suggestions were reduced to approximately 50 focused topics for research. Most of the projects suggested fell into three categories: epidemiology and epidemiologic methods; toxicology; and sampling, analysis, and exposure assessment. In addition, projects in areas labeled

“clinical,” “occupational,” and “dosimetry” were identified. More than half a dozen practical suggestions were also offered. When examined in toto, the suggestions imply that a great deal can still be learned about linking exposure to particulate matter with human health. Some of the research is costly—perhaps impossibly so—unless new approaches, better coordination, and increased funding occur. However, the list of suggestions represents a coordinated attack on understanding the associations between particulate air

pollution and human health. Also, one is struck with the practicality of the suggestions, as none appear to be unrealistic, given our current scientific expertise. The research, if substantially conducted, can be applied to providing a more healthful future for people everywhere.

#### References

1. Phalen, R.F.; McClellan, R.O.; PM10 Research Needs. *Inhal. Toxicol.* 7(5):773-779 (1995).