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

March 1, 2004

OFFICE OF THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

EPA-SAB-CASAC-04-005

The Honorable Michael O. Leavitt
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Subject: Clean Air Scientific Advisory Committee (CASAC) Particulate Matter (PM) Review Panel's Ongoing Peer Review of the Agency's *Fourth External Review Draft of Air Quality Criteria for Particulate Matter* (June 2003)

Dear Administrator Leavitt:

EPA's Clean Air Scientific Advisory Committee (CASAC), supplemented by expert consultants — collectively referred to as the CASAC Particulate Matter (PM) Review Panel ("Panel") — met via public teleconference on February 3, 2004 to discuss follow-on matters related to its ongoing peer review of the two-volume, June 2003 draft document, *Fourth External Review Draft EPA Air Quality Criteria for Particulate Matter* (EPA/600/P-99/002, aD, bD).

This teleconference meeting was a continuation of the CASAC PM Review Panel's review of the Fourth External Review Draft of the Air Quality Criteria Document (AQCD) for PM in the current cycle for reviewing the National Ambient Air Quality Standards (NAAQS) for PM. Specifically, the Panel deliberated on the major revisions (December 2003) to Chapters 7 (Toxicology of Particulate Matter in Humans and Laboratory Animals) and 8 (Epidemiology of Human Health Effects Associated with Ambient Particulate Matter) of this draft document.

As noted below, it was the consensus of the Panel that, while these two updated chapters are substantially improved, they still require further revision in order to provide an appropriate summary of the policy-relevant science in these two subject areas. A subsequent meeting of the Panel will be planned to review the remaining issues related to Chapters 7, 8 and 9 (Integrative Synthesis).

1. Background

The CASAC was established under section 109(d)(2) of the Clean Air Act (CAA or "Act") (42 U.S.C. 7409) as an independent scientific advisory committee, in part to provide advice, information and recommendations on the scientific and technical aspects of issues related

to air quality criteria and national ambient air quality standards (NAAQS) under sections 108 and 109 of the Act. Section 109(d)(1) of the CAA requires that EPA carry out a periodic review and revision, where appropriate, of the air quality criteria and the NAAQS for "criteria" air pollutants such as PM. The CASAC is administratively located under EPA's Science Advisory Board (SAB) Staff Office.

EPA is in the process of updating, and revising where appropriate, the AQCD for PM as issued in 1996. The history of this current, ongoing review is contained in the Background section of the Panel's most recent report on this subject from the public meeting held in Research Triangle Park (RTP), NC, on November 12-13, 2003 (EPA-SAB-CASAC-04-004, dated February 18, 2004). The roster of the CASAC PM Review Panel is found in Appendix A to this report.

2. CASAC PM Review Panel's Ongoing Review of the *EPA Air Quality Criteria for Particulate Matter (Fourth External Review Draft)*

The CASAC PM Review Panel met via teleconference on February 3, 2004 to review the December 2003 major revisions to the drafts of Chapters 7 (Toxicology) and 8 (Epidemiology) of the Fourth External Review Draft of the AQCD for PM that had been revised based on the discussions and report of the Panel's public meeting held August 25-26, 2003. It was the consensus of the Panel that these chapters are substantially improved, but still require further revision in order to provide an appropriate summary of the science in these two areas. The review comments of individual panel members are presented in Appendix B to this report. The Panel's consensus comments on these chapters are summarized below.

Chapter 7 (Toxicology)

The chapter has been significantly improved with the last set of revisions that were made. The introductory material on the interpretability and implications of various variables measured in cardiovascular studies is excellent. This material allows the reader to have a better grasp of the potential significance or lack thereof of the various studies that are discussed later on in Section 7.2. The addition of more exposure data throughout the chapter is helpful, but there are still some studies for which this information is not supplied. It is essential that this information be included for any studies that are to be cited in the document.

There has been material on bioaerosols added, but it includes some material that, if provided earlier in the development of the PM AQCD, would probably have gone into earlier chapters. Thus, it is suggested that the chapter focus on the toxicology of the bioaerosol and its implications for the health effects of ambient particulate matter, particularly coarse particles. The other material could go into an appendix to this chapter. This appendix can provide the context for the toxicology of ambient bioaerosols. The key to this section is to clearly indicate the likelihood that biological components of PM are contributing to the observed respiratory and possibly cardiovascular system effects. Clearly, if it is the biological components in the ambient aerosol that play a large role in the induction of adverse health effects, then very different policy questions arise compared to case where the impacts arise from sources amenable to emission controls.

The recently-added Appendix to Chapter 7 makes a good start on the extrapolation of rat to human doses, but does not yet achieve the goal of providing clear comparisons of rat and human doses if both species were exposed to the same aerosol concentration with the same particle size distribution for given periods of time. Rather, Appendix 7A has the tone of being an effort to defend the use of high instillation doses in animal studies and to infer that all high exposure levels in animals produce relevant results for humans. This is particularly the case because most of the emphasis is on total mass deposited or retained calculations rather than what most toxicologists would view as more relevant dose metrics. In addition, relative to mass, total mass is the only dose metric implying animals should be exposed to higher concentrations than humans to achieve equivalent dose, at least for fine mode particles.

There needs to be improvement in the description of the model parameters and exposure conditions (*e.g.*, moderate work *vs.* resting) on which the extrapolations are based in order to guide the sequence of the material that is presented. First, a comparison should be made for rats and humans exposed to the same concentration level and particle size distribution for the same period of time. Then, scenarios could be presented for what the human exposure scenario would be to achieve the same dose metric (*e.g.*, mass per unit area in the alveolar region) to match what a rat exposure scenario. With this as background, the reader would now be able to appreciate the comparisons on specific studies such as the Utah Valley study or one of the concentrated airborne particles (CAP) studies. The Appendix to Chapter 7 also suffers from "information overload" in the tables.

Material should be added to the Appendix that provides a rationale as to how the different dose metrics may relate to different biological endpoints. Are there effects that should relate to total mass in the lung rather than mass per unit surface area? What about dose metrics in a single macrophage? (Note: Only a small percentage of alveoli have particles depositing in them. The particles deposit preferentially in the first few generations beyond the terminal bronchi.) The tables are very difficult to follow, and some of the numbers in them appear to arise from different exposure scenarios than those stated. There are a number of other details in Appendix 7A that require careful attention. In particular, PM Review Panelist's individual comments found in Appendix B to this report raise a number of issues regarding the material in Appendix 7A and provide a number of useful suggestions for improving the presentation of this material.

One important issue that needs to be considered when discussing earlier studies with PM and contrasting them with newer studies, is the use of healthy animals in earlier work versus increasing use of animal models of compromised human conditions in later studies. This is key when evaluating PM effects, and yet at the same time it creates a difficulty of selecting a "relevant" animal model in terms of the pathophysiology of a human disease. Much too often the (tacit) assumption is made that high and higher doses (exposure concentrations) used in healthy animals make up for a compromised organ function, an assumption that needs experimental validation. Mechanisms of PM effects are most likely quite different in both situations. It will be useful to add a sentence on the necessity to establish animal models of susceptibility for future studies.

Chapter 7 must make it clear that there is a large database that indicates that particulate matter is markedly variable in its toxic potency. Some PM is found to be relatively inert while

other PM components have readily-measurable toxic properties in different experimental systems. Moreover, it is apparent that some of the variation in toxic potency is attributable to differences in PM properties such as composition and size. Of the many different kinds of PM studied, Residual Oil Fly Ash (ROFA) may be unique in its toxic properties and not very representative in toxicity or mode of action of many other kinds of PM. Thus, it is hard to accept generalizations based on studies of unusual PM such as ROFA. There also needs to be a clearer indication that CAPs are not a well-defined material, and vary from location to location and time to time at a given location. They are useful in that they represent real-world particles, but they do not provide the kind of reproducible exposures that are typically used in toxicological studies.

It is essential that there be clearer documentation in Chapter 7 for scientific conclusions regarding the toxicological mechanisms identified in laboratory studies so they can be carried forward to the revised integrative synthesis (Chapter 9) that is yet to be presented to the Panel.

Chapter 8 (Epidemiology)

This revised draft is substantially improved over the previous draft. The Overview of the key methodological issues is now better focused and directed toward the issues that are covered in the Chapter, rather than a more textbook orientation toward the subject of epidemiology. This makes it more relevant and readable. In the discussion of confounding and effect modification, it is suggested that there should be reference to the more extensive discussion of the problem of exposure misclassification that is provided later in the chapter.

There was further improvement in the evenhandedness of the discussions. The sections on time-series studies of hospitalizations and on effects on measures of cardiovascular "physiology" (p.153) are particularly improved in this regard. However, further improvement is possible. For example, the time-series studies of Canadian hospitalizations of Burnett *et al.* — studies in which is was found that the effects of the gaseous pollutants overwhelmed those of PM — were criticized by noting that selection of day lags is "completely data driven" (p.140, line 16; p.141, line 13). This same criticism could have been leveled at almost every other time-series study reviewed in this chapter, but was not. Further, regarding the National Morbidity, Mortality and Air Pollution Study (NMMAPS) overall effect estimates, a somewhat mixed message is conveyed. It is initially stated (p.36, line 13) that NMMAPS provides "extremely useful information regarding ... the magnitude of the combined PM_{10} effect estimate." Later (p.46, line 17) it is stated that this estimate "may well underestimate the PM_{10}-total mortality effect size suggested by two other well conducted multi-city studies..." (effects based on much smaller numbers of cities) and that it reflects overaggressive control of temporal trends (p.47, line 1). This mixed message is confusing.

There is now some discussion in the text of revised generalized additive model (GAM) individual-city studies. However, the discussion of the changes in risk estimates arising from the revised GAM analyses presents the results in a rather confusing manner. It is suggested that the changes in mortality effect estimates be presented as percent changes in the effect estimates, as they are for hospitalization.

This draft incorporates the new important findings based on the Hoek *et al.* report from the Netherlands on the association between residence in proximity to large roadways and mortality. Care must be taken in reporting the estimate of effect from this study of black smoke based on background concentrations, since the unadjusted estimate (the estimate reported in the PM AQCD), the adjusted estimate (the estimate most comparable to other cohort studies), and the estimate based on long-term residents only, are all provided in the paper.

Section 8.2.3.1.2 (p. 8-81) introduces the semi-individual chronic exposure studies without informing the reader about the key characteristics of the populations and how they influence later interpretations of the findings concerning applicability to standard setting. This is especially important in relation to the American Chemical Society (ACS) and Harvard "Six-Cities Study" cohorts because they provide key information informing the annual $PM_{2.5}$ NAAQS. It should be noted, in this section, that the Six-Cities cohort was pre-selected, by the investigators, to be a representative population, at least for the region of the country that was (is) heavily-impacted by both coal combustion and motor vehicle effluents. By contrast, the ACS study cohort is drawn from a large pool of volunteers who happened to live in communities where several years of fine particle and/or sulfate ambient air concentration data were available. It is important to note that the ACS had a relatively small proportion of people with less than high school education (12% vs. 28% for Six-Cities) and, by inference, better diets and access to good health care than an average U.S. population. To the extent that the mortality impact is lower in the better educated portion of the population, the mortality experience of the ACS cohort provides an underestimate for the U.S. population as a whole.

By comparison, Section 8.2.3.2.3 (p. 8-99) on the Adventist Health and Smog (AHSMOG) Study cohort, and Section 8.2.3..2.4, on the Electric Power Research Institute (EPRI) Veterans cohort (p. 8-103) do introduce the special attributes of these two other cohorts.

In Section 8.2.3.2.5 on the relationships among the four cohort's findings (p. 8-106 and in Table 8-11), there should be some discussion of the effects of the nature of the cohort selection on the differences in reported relative risks (RRs). In the summary of the cohort studies (pp.124-7), there was no mention of the Pope ACS extended analysis findings (JAMA 2002), particularly with regard to lung cancer.

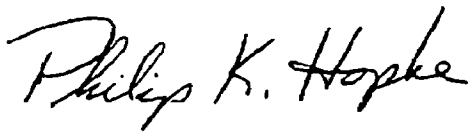
As part of the discussion of the cohort study results, the AHSMOG and Veterans study are dismissed without an adequate basis. The discussion of the Lipfert and Morris study (p. 115, line 4) is confusing. It is noted that variables for some potentially relevant ecologic factors are included in their models and that this may explain their generally lower estimates of effect compared to the cohort studies. Is this appropriate adjustment for confounding, or is this "overadjustment" and that the resultant estimates should be discounted? If these studies are to be discounted, the arguments presented must be much clearer.

A number of specific comments were provided by the panel members in Appendix B to this report. It was noted by several Panel members that some of the specific errors identified in the prior review have carried over into this version. We request that careful attention be paid to the prior comments as well as the specific comments provided here so that as many of these minor errors can be corrected before the chapter is again reviewed.

Closing Comments

In closing, the CASAC PM Review Panel recognizes the complexity of the challenge faced by EPA staff and the outside contributors to Chapters 7 and 8 of the revised PM AQCD, and the tight time constraints they faced in responding to the numerous technical comments on these and earlier drafts of these chapters by both members of the Panel and representatives of the public. Interpretation of such a large body of peer reviewed literature — much of it based on studies that were not designed nor intended for application to standard setting, and which often appear to be inconsistent with the results of other studies — requires both broad perspectives and careful attention to details. The Panel members appreciate the hard work and sincere efforts of the authors, and offer the constructive comments in this letter and those from previous reviews of earlier drafts in order to help the Agency meet its statutory obligations for timely periodic reviews of peer-reviewed scientific knowledge relevant to standard setting. As always, the Panel wishes the Agency well in this important endeavor.

Sincerely,



Dr. Philip K. Hopke, Chair
Clean Air Scientific Advisory Committee

Appendix A – Roster of the CASAC Particulate Matter Review Panel

Appendix B – Review Comments from Individual CASAC Particulate Matter Review Panelists

Appendix A – Roster of the CASAC Particulate Matter Review Panel

U.S. Environmental Protection Agency
Science Advisory Board (SAB) Staff Office
Clean Air Scientific Advisory Committee
CASAC Particulate Matter Review Panel*

CHAIR

Dr. Philip Hopke, Bayard D. Clarkson Distinguished Professor, Department of Chemical Engineering, Clarkson University, Potsdam, NY

Also Member: SAB Board

CASAC MEMBERS

Dr. James D. Crapo, Chairman, Department of Medicine, and Executive Vice President of Academic Affairs, National Jewish Medical and Research Center, Denver, CO

Dr. Frederick J. Miller, Vice President for Research, CIIT Centers for Health Research, Research Triangle Park, NC

Mr. Richard L. Poirot, Environmental Analyst, Air Pollution Control Division, Department of Environmental Conservation, Vermont Agency of Natural Resources, Waterbury, VT

Dr. Frank Speizer, Edward Kass Professor of Medicine, Channing Laboratory, Harvard Medical School, Boston, MA

Dr. Barbara Zielinska, Research Professor, Division of Atmospheric Science, Desert Research Institute, Reno, NV

CONSULTANTS

Dr. Jane Q. Koenig, Professor, Department of Environmental Health, School of Public Health and Community Medicine, University of Washington, Seattle, WA

Dr. Petros Koutrakis, Professor of Environmental Science, Environmental Health, School of Public Health, Harvard University (HSPH), Boston, MA

Dr. Allan Legge, President, Biosphere Solutions, Calgary, Alberta

Dr. Paul J. Lioy, Associate Director and Professor, Environmental and Occupational Health Sciences Institute, UMDNJ - Robert Wood Johnson Medical School, NJ

Dr. Morton Lippmann, Professor, Nelson Institute of Environmental Medicine, New York University School of Medicine, Tuxedo, NY

Dr. Joe Mauderly, Vice President, Senior Scientist, and Director, National Environmental Respiratory Center, Lovelace Respiratory Research Institute, Albuquerque, NM

Dr. Roger O. McClellan, Consultant, Albuquerque, NM

Dr. Günter Oberdörster, Professor of Toxicology, Department of Environmental Medicine, School of Medicine and Dentistry, University of Rochester, Rochester, NY

Dr. Robert D. Rowe, President, Stratus Consulting, Inc., Boulder, CO

Dr. Jonathan M. Samet, Professor and Chair, Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD

Dr. Sverre Vedal, Professor of Medicine, National Jewish Medical and Research Center, Denver, CO

Mr. Ronald H. White, Research Scientist, Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD

Dr. Warren H. White, Visiting Professor, Crocker Nuclear Laboratory, University of California - Davis, Davis, CA

Dr. George T. Wolff, Principal Scientist, General Motors Corporation, Detroit, MI

SCIENCE ADVISORY BOARD STAFF

Mr. Fred Butterfield, CASAC Designated Federal Officer, 1200 Pennsylvania Avenue, NW, Washington, DC, 20460, Phone: 202-564-4561, Fax: 202-501-0582, (butterfield.fred@epa.gov) (FedEx: Fred A. Butterfield, III, EPA Science Advisory Board (1400A), Ariel Rios Federal Building North, Suite 6450, 1200 Pennsylvania Ave., NW, Washington, DC, 20004, Tel.: 202-564-4561)

* Members of this CASAC Review Panel consist of:

a. CASAC Members: Experts appointed to the statutory Clean Air Scientific Advisory Committee by the EPA Administrator; and

b. CASAC Consultants: Experts appointed by the SAB Staff Director to serve on one of the CASAC's National Ambient Air Quality Standards (NAAQS) Review Panels for a particular criteria air pollutant.

Appendix B – Review Comments from Individual CASAC Particulate Matter Review Panelists

This appendix contains the preliminary and final written comments of individual members of the Clean Air Scientific Advisory Committee (CASAC) Particulate Matter (PM) Review Panel who submitted such comments electronically. The comments are included here to provide the all suggested edits, a full perspective, and range of individual views expressed by Subcommittee members during the review process. These comments do not represent the views of the CASAC PM Review Panel, the CASAC, the EPA Science Advisory Board, or the EPA itself. The consensus views of the CASAC PM Review Panel and the CASAC are contained in the text of the report to which this appendix is attached. Panelists providing comments are listed on the next page, and their individual comments follow.

Panelist	Page #
Dr. Frederick J. Miller	B-3
Dr. Frank Speizer	B-7
Dr. Barbara Zielinska	B-10
Dr. Jane Q. Koenig	B-12
Dr. Petros Koutrakis	B-14
Dr. Paul J. Lioy	B-15
Dr. Morton Lippmann	B-17
Dr. Joe Mauderly	B-23
Dr. Roger O. McClellan	B-32
Dr. Günter Oberdörster	B-44
Dr. Jonathan M. Samet	B-52
Dr. Sverre Vedal	B-54
Mr. Ronald H. White	B-58
Dr. Warren H. White	B-61
Dr. George T. Wolff	B-63

Dr. Frederick J. Miller

Fred J. Miller, Ph.D.
February 1, 2004

Comments on Chapter 6 – Dosimetry of PM

General Comments -- The changes that have been made to the chapter have for the most part strengthened the chapter. The appropriate caveats have been added and there are only a few specific changes that should still be made. The specific comments below indicate what changes or clarifications are needed. Once they are addressed, I would recommend closure to the full CASAC.

Specific Comments

p. 6-32 The text contained on lines 14-16 is messed up and needs redoing.

p. 6-46 The Crapo et al. (1982) reference is an old one. Crapo and colleagues (Stone et al., 1992, Am. J. Respir. Cell Mol. Biol. 6: 235-243) have more recent data on cell type, number and percentages that should be referenced. I do not believe the 3-19 range for the percentage of alveolar macrophages in healthy, normal humans, and other mammals is the correct range.

p. 6-89 Suggest changing the text to read "from the National Institute of Public Health and the Environment of the Netherlands (RIVM),".

p. 6-91 The statements about the differences between the LUDEP and MPPD models are made as generalizations that should be made more specific or made with a likely explanation for the difference. For example, on line 6 the main reason for the lower TB deposition with the MPPD model is that the total deposition curve is shifted slightly to the right for the MPPD model compared to the LUDEP model. Also, the shift to a slightly lower TB deposition fraction results in a higher alveolar region deposition. But probably the main reason for the differences between the models is that the LUDEP uses a rigid lung structure while the MPPD accounts for the expansion and contraction of the lung during breathing.

p. 6-95 In Table 6-5, the order of results should be maintained across the table. So the columns each time would go ICRP, MPPD, and the Ratio. Having the two ration columns side by side for nose breathing and then later in the table for mouth breathing is confusing.

Fred J. Miller, Ph.D.
February 9, 2004

Comments on Chapter 7 -- Toxicology of PM in Humans and Laboratory Animals

General Comments -- The chapter has been significantly improved with the last set of revisions that were made. The introductory material on the interpretability and implications of various variables measured in cardiovascular studies is excellent. This material allows the reader to have a better grasp of the potential significance or lack thereof of the various studies that are discussed later on in Section 7.2. The addition of more exposure data throughout the chapter is helpful, but there are still some studies for which this information is not supplied. While the material added on bioaerosols is interesting reading, the punch line relative to the interpretation of PM studies and the regulatory implications of bioaerosols for PM 10-2.5 or PM 2.5 standards does not come across in the chapter.

The interpretative summary (Section 7.7) is, in general, well written and much improved over earlier drafts. However, the subsection on Bioaerosols (Section 7.7.2.6) comes to no conclusions as to the links between bioaerosols and PM health effects.

The Appendix to Chapter 7 on rat to human dose extrapolation is a good start but falls short of achieving the goal of providing clear comparisons of rat and human doses if both species were exposed to the same aerosol concentration for a given period of time. Rather, the Appendix comes across as an effort to defend the use of high instillation doses in animal studies and to infer that all high exposure levels in animals produce relevant results for humans. This is particularly the case because most of the emphasis is on total mass deposited or retained calculations rather than what most toxicologists would view as more relevant dose metrics. In addition, relative to mass, total mass is the only dose metric implying animals should be exposed to higher concentrations than humans to achieve equivalent dose, at least for fine mode particles.

Material should be added to the Appendix that provides a rationale as to how the different dose metrics may relate to different biological endpoints. Are there effects that should relate to total mass in the lung rather than mass per unit are? What about dose metrics in a single alveolus or macrophage? The tables are very difficult to follow and some of the numbers in them appear to arise from different exposure scenarios than what are stated.

The authors can do a better job of laying out the extrapolation considerations by the order in which material is presented. First, a comparison should be made for rats and humans exposed to the same concentration level for the same period of time. Then scenarios could be presented for what the human exposure scenario would be to achieve the same dose metric (e.g., mass per unit area in the alveolar region) as what a rat exposure scenario yielded. With this as background, the reader would now appreciate the comparisons on specific studies such as the Utah Valley study or one of the CAPs studies. The Appendix also suffers from information overload in the tables.

Specific comments

p. 7-179-80 Kevin Dricoll's name is spelled incorrectly.

p. 7A-3 On line 11, insert a comma after "metric"; insert a semicolon after "parameter"; insert a comma after "thus". In Table 7A-1, the row relating to surface area as the PM indicator should include alveolar as well as tracheobronchial.

p. 7A-4 I believe equation 2 has not been previously published, so the equation should be eliminated or else a reference provided. On line 16, the wrong reference to the MPPD model is cited. On line 25, suggest the wording be changed to read "who breathe increasingly through the mouth when activity level requires more than about 35 $Lmin^{-1}$ (Niinimaa et al., 1981)". The Niinimaa reference is Respir. Physiol. 43: 69-75.

p. 7A-5 As part of the reference to Table 7A-2, the text should indicate that the PM burden concept statement refers to nonoverload exposure levels. On line 13, change oral-nasal to oronasal.

p. 7A-6 Clarify what normalization is being used for Figure 7A-1,b.

p. 7A-7 On line 13, the number 0.275 is not likely accurate to these number of digits. For the calculations presented here, was the inhalability adjustment in MPPD used? On line 25, the authors should make it clear that the time to achieve equilibrium is a function of the exposure level.

p. 7A-9 The figure on this page is confusing. Does the Rat (100) in Panel A refer to the value for the rat having been multiplied by 100? For the Y axis, the variables used do not easily lead to the units that are presented. Some clarification in the legend would be helpful.

p. 7A-10 In Table 7A-5, the exponent on m should be a smaller font and clearly be an exponent.

p. 7A-11 Concentration ration and DAF ration are not the same since time is not included yet clearance is included in the scenarios presented.. On lines 16-30, it is not clear how the calculations were done since the MPPD model does not currently handle variable exposure concentrations.

p. 7A-12 Some entries in this table are confusing. DAF can not be calculated for retained mass as it is only meaningful for deposition. The same comment applies to Table 7A-7.

p. 7A-13 On line 5, the only relevant diameter in this listing is that of aerodynamic diameter.

p. 7A-14 The wording appears to be messed up on the first few lines.

p. 7A-15 Too many scenarios are presented in Table 7A-8. The reader would probably follow easier if the material was split into at least two tables.

p. 7A-16 On line 20, is the reference to mass or particle number. Clarification is needed.

p. 7A-19 Again, the reader is being misled with the emphasis on total mass rather than mass per unit area.

p. 7A-20 On line 15 the word "be" should instead be "been"

Comments on Chapter 8 – Epidemiology of Human Health Effects Associated with Ambient Particulate Matter

General Comments –

This version of Chapter 8 is greatly improved over previous versions. There is a better balance of presentation of the science without the implication of endorsement of a particular viewpoint. The only specific comments I have relate to the discussion of thresholds in Section 8.4.6. where there appears to be a bias for linearity that emerges by the way the text is written in multiple areas.

Specific Comments

p. 8-253 The grid used in the search for thresholds (as cited on line 22 of page 8-253) was too coarse for the resolution sought by the Agency in the standard setting process. For example, the grid increments represent 33% of the level of the current fine mode annual average standard. If the Agency is contemplating revisions, then the grid would need to be in increments of 2 $\mu g/m^3$ or so.

p. 8-254 Seven of the nine curves presented in Figure 8-23 are nonlinear. Yet the text describes the trend as supporting a linear association. I find this troublesome since the magnitude of the risk estimates have already been shown in the draft Staff Paper to be primarily driven by the way thresholds are or are not treated.

p. 8-255 On lines 9-10, the text states that Cakmak et al. (1999) did various analyses and concluded that "if threshold exists, it is highly likely that standard statistical analysis can detect it." Yet in the next paragraph (line 21) the statement is made that comes across quite biased wherein the authors write "These results, if they in fact reflect reality, make it difficult to evaluate the relative roles of different PM components (.... Here the discussion is referring to thresholds.

p. 256 The tendency to dismiss the possibility of a threshold for mortality is again stated as "...., but meanwhile, the use of linear PM effect model appears to be appropriate".

Dr. Frank Speizer

Frank Speizer's Comments on Revised Chapters 7 & 8 of CD dated December 2003

Chapter 7

General Comment: I will make no attempt to comment in detail on the text. My comments relate mostly to reviewing the chapter as a summary. I found it much improved in its outline and flow. The tables are well constructed. I would have liked to see a number of summary figures or tables at the conclusion of each section with some of the most important findings highlighted. In the interpretive section it might have been useful to separate off in a table the findings in human controlled exposure studies. These, from my perspective are much closer to my needs of understanding the potential mechanisms, and would have given me a better judgment of how many more such studies are necessary. In addition, simply because these are in humans the dose exposures would be more relevant to understanding how they might related to ambient exposures.

Review of Chapter 8

General Comment: The Overview of the key methodological issues is now seemingly focussed and directed toward the issues that are covered in the Chapter, rather than a more textbook orientation toward the subject of epidemiology. This makes it more relevant and readable.

Although the two paragraphs on page 8-14 that discuss "biologically-plausibility based models" are reasonable, they do not really provide the insight that might be judged by their relevance.

Bottom of page 8-47, top of page 8-48: This is a nice summary of the effects of model specification on the multi-city estimates. I wonder if it might be useful to specify at this point the range of effects that would indicate; just how conservative the increased specification of potential risk modifications makes the estimates.

In contrast to the section on multi-city studies the details on the single city studies reads more like a catalogue of the studies reported with little interpretation. The difficulty here is that the statements indicate that there are some data on PM10-2.5 but little is discussed. The summary however, on page 8-52 suggests that the PM effects persist (although which PM we will have to wait to read about) and we will hear more about it as we move through the chapter. Whether a summarizing Table here would be useful should be considered.

Section starting at 8.2.2.5 probably belongs in Chapter 9 (and Staff paper). As long as it is here as an introduction to section on size that is ok, but I would be cautious about suggesting that comparisons of effects of PM across sizes will be part of this discussion here.

Page 8-61, line 19-21: These two sentences are inconsistent. The first says "no" the second says "yes". Need to modify.

Page 8-64, after line 6: It might be useful to summarize here the effects of size. What has been covered suggests that the source that produces the particle mix may be important. Given the data from the east of US vs. west of US; the correlations with PM2.5 may be different, and given data from Germany that uncontrolled coal burning makes SO2 a surrogate for particles of different sizes

Page 8.79 line 28-31. Another sentence is required to indicate that there is a lack of data rather than simply "...do not support increase mortality risk..."

Page 8.81, line 7: The use of the term "semi-individual" is pure jargon. It is very unclear what this means. The cohort studies reviewed are of individuals in whom personal characteristics are known, the pollution measures are regional or environmental (rather than personal) the data collection is mostly prospective, and that is what we know about what the cohort studies mean. Suggest simply leave out "semi-individual".

Page 149, line 23: I simply may have missed it but if the "(see above)" refers to something in this section on Cardiac Physiology, OK, but if it is referring to much earlier in the text, then it needs to be defined again here.

Page 8-153, para. lines 15-27, and last sentence: I am not sure the word "discrepancies" is appropriate here. The results are varied, the populations differ, and consistency is not apparent, but I do not interpret this as discrepant. There is simply not enough work reported yet. I also do not think the sentence should damn with really lack of faint praise all ECG measures of cardiovascular parameters, since many such as ST segment change, T wave alternans, etc. were not even mentioned. (This is mentioned specifically here because in the next section the conclusion on blood markers seems stronger with even less data).

Section 8.4.3.2 and 3: These more conceptual issues seem overdone here. In particular there is previously a section on intervention studies that indicate the very few studies that exist. To indicate that this is a "third promising approach" to solving a conceptual issue seems a little strong.

Page 8.260 Section ending here. Although this discussion is important I am concern it leaves the wrong impression. The conclusion in each section seems to end like this one in that evidence is insufficient about the variation seen. It seems to me that given the number of unknowns the fact that one gets a relatively consistent finding at least in terms of direction that the variations in magnitude really must relate to a host of unknowns and as such is really part of the "noise" in estimating a level of effect. This will not make our job any easier in trying to come up with a regulatory number, but it certainly should take us out of the realm of worrying about whether the effect is real. I think this needs to come through a little stronger, and let us do the more speculative and negotiation in the Staff paper rather than here.

Page 8.282 Simply for balance since this is the end of the section on the strengths and limitations of the 6-city study and the ACS study, one needs at least a cross reference to or a summary here of the Loma Linda and VA studies.

Dr. Barbara Zielinska

Review of revised Chapter 7 of PM Criteria Document

Barbara Zielinska

I did not review the previous version of Chapter 7, so I don't know if this revised version offers any improvements. However, I have several comments regarding this version, which are detailed below:

1. Section 7.2, page 7-10, lines 9-12: it says that Table 7-1a and 7-1b summarize newly available studies...of ambient PM or surrogate PM. However, most of the studies cited in Table 7-1a refer to ROFA that can hardly be regarded as relevant to ambient PM. The particle sizes shown for some of the CAP's studies presumably refer to the lower size limit (such as 0.2 to 0.3 um). The limitation of these studies was that particles smaller than 0.1 – 0.2 um could not be concentrated efficiently by CAP models that were used at that time, and thus a large portion of combustion generated particles (such as diesel, wood smoke, gasoline vehicles, etc.) were excluded.
2. Page 7-20, line 10-23. The exposure to 15 mg/m3 of ROFA is probably 1000 or more (not 100) higher than usual current U.S. ambient concentrations, taking into account that ROFA chemical composition may account for a few percent (or less) of ambient PM.
3. Page 7-22, line 28: seen, not seem
4. Section 7.3.1, Table 7-2a. Again, particle sizes listed for some CAP's studies presumably refer to the lower particle size limit and ranges from 0.2 to 0.65 um. No particles smaller than 0.2 um are listed, which eliminates an important part of the primary combustion particles. Also, the same table cites the study from Utah Valley that used 10 years old PM10 filters. It is interesting to note that the U.S.EPA methods limit the time between a PM sample collection and its extraction and analysis to 2 months, in order for the results to be considered fully valid, and in the health study 10 years old sample is still regarded as a valid sample.... The discussion on page 7-40 and 7-41 regarding this study doesn't mention this long storage period; it does say however, that the filters were stored in plastic sleeves at room temperature and humidity. These storage conditions (for 10 years!) are unacceptable and contrary to all QA/QC practices; filter samples should be stored in a freezer and in the dark! The study seems to have more problems: 70% of mass in the extracts appeared to be derived from the glass filter matrix??
5. Page 7-43, line 20-27. The statement: "The fact that instillation of ambient PM collected from different geographical areas and from a variety of emission sources consistently caused pulmonary inflammation and injury tends to corroborate epidemiological studies that report increased PM-associated respiratory effects in populations living in many different geographical areas and climates" is not necessary supported by the data discussed in this section. Most of the discussion refers to ROFA, other oil combustion emission PM, Utah Valley (which has some problems) and NIST SRM 1648 (St. Louis

sample collected in the early 1980s over a year or longer). The SRM material was not intended as a PM sample for the health study; it was created for analytical purposes.

6. Section 7.3.1.2, Diesel Particulate Matter. Page 7-47, line 12-28, what is the value of this poorly characterized study? Also, p 7-49, line 19-28, the diesel emissions (not only DPM, but also gaseous emissions) level for the cited study was very high, and cannot really be compared to ambient PM levels!
7. Section 7.3.4. The addition of Bioaerosol section is certainly very useful and appropriate. Some of the material, especially concerning atmospheric levels of cellulose/other plant debris markers belongs to other chapters, but since it is not there, it is okay to keep it here...
8. Section 7.4. I don't see any reason to have Table 7-8 here, especially that it is not very informative...
9. Page 7-116, line 20-25. The gas-phase compounds, listed as found in diesel exhaust, are present in gasoline vehicle exhaust in comparable or higher concentrations (i.e. benzene, ethylene, 1,3-butadiene, etc).
10. Page 7-125. There is an error in equation 2.
11. Table 7-12. There is an error in the first entry – O3 should not be listed under particle size.
12. Section 7.7 – Interpretive Summary. I find the discussion on p. 7-169- 170, line 18 to the end, confusing. Why the comparison is made for a healthy human working near "busy road"? I agree with some of the Public Comments that the comparative dose analysis carried out in Appendix A, with conclusions presented in section 7.7, should be subjected to more through peer-review by the experts in this area. I'm not sure that the conclusion on page 7-170, that "...the high exposure concentrations and instillation doses in the rat provide a useful and relevant approach..." is truly justified.
13. Page 7-172, line 15-29. The statement about the generic "combustion-related PM" is not correct. There is a big difference in a chemical composition between ROFA, diesel PM, gasoline vehicle PM, etc. To lump them all together as fossil fuel combustion products, and say that they represent ambient PM, is misleading. On the one hand, the authors of this chapter recognize that not all ambient PM is created equal, but on the other hand, it is not always clear.
14. Page 7-184, line 10-15. The text says that the organic compounds remain a potential casual property for PM due to the contribution of diesel exhaust to the fine PM fraction. It fails to acknowledge that the other sources of organics, such as gasoline vehicle PM, wood smoke, etc., are equally important.

Dr. Jane Q. Koenig

Janaury 2004 response to revised chapter 7 and 8
1-20-04

Jane Q Koenig

Chapter 7
I have no further comments on this chapter. I deem it satisfactory for inclusion in the final CD.

Chapter 8
I agree with Mort Lippmann and Jon Samet that this Chapter needs no further editing (beyond the minor changes they recommend).

I do have a few minor comments as well.

8-57 Why is the RR for death at 1 day lag in Mar et al, so much higher that the other studies??

8-62 The correlation between ultrafine particles and mass concentrations should include a comment on whether the correlation include spatial ultrafine data or only data from one site. It appears in Seattle that UF are not distributed according to the same spatial pattern as PM2.5.

8-68 It might be good to reference Thomas Lumley's presentation on the problems involved with using source apportionment data in health studies that he presented at AAAR in April, 2003. I think this would also allow woodsmoke to be mentioned as a source of growing interest.

8-128 Its probably too late now, but a primer on cardiovascular health end points would be a nice additional to the next CD. There is a good figure on HRV in Stone and Goleski, Am Heart J 138 (5).

8-146 Fig 8-10. Are the wide CIs from the Ito study simply due to smaller sample size?If so it would be useful to state that.

8-166 Does table 8-20 add anything formation that isnt in Table 8-19?

8-174 table 8-22 doesn't match the earlier Tables? Can RR be used here?

8-184 Personally I do not like to use of MC for micron--if that is what it is? When did that get initiated?

8-218 I agree with Jon Samet that this paragraph does not portray the extent of the scientific knowledge regarding gaseous pollutants. Also the statement that health effects to not appear to occur in healthy individuals is true for PM effects as well. Although mainly, the effects of air pollution in healthy adults has not be studied.

8-288 Should new studies on diabetes be mentioned here? Also intervention studies as a category?

8-291,92Under (8). The conclusion adds a caveat that HR and blood markers provide only limited support for PM-related cardiovascular effects. There is no doubt about the cardiovascular effect, the limited support is confined to understanding the mechanisms of the CV effect. It that clear from the wording at the end of this section?

8-294 (15). This conclusion would be strengthened it other intervention studies were summarized here. Clancy, Friedman, eg. Perhaps (15) and (16) should be merged to make one strong point.

8-295 I cant believe that adverse health effects of children wasn't an extremely important area of concern in 1996. Maybe this should be reworded to stating health effectds of pre and post natal periods are now emerging.

Congratulations on a tremendous endeavor.

Dr. Petros Koutrakis

Review of Chapter 7 by Petros Koutrakis:
Date: February, 5, 2004

Overall I think that the authors did an excellent job and I disagree with many comments made by the committee:

1) The CD should include a thorough review of the literature for the period 1997 to date. The authors prepared a comprehensive review and include everything I am aware of. I really enjoyed reading this chapter and certainly learned a lot. Going back to early 90s is waste of people's time. I think there is a point where we should stop abusing EPA and their consultants.

2) I thought the authors stressed the advantages and shortcoming of the different approaches and were very careful not to over interpret results. We need to remember that the authors neither designed nor conducted the reported studies so it is not their problem if we do not like certain toxicological approaches. I think where we should be critical is the conclusions drawn from the reported results. This will be done at the last chapter and it remains to be seen whether there is a sound and objective review of the literature.

3) I think we keep criticizing toxicology for failing to create the undisputable evidence for supporting the epidemiological results. The bar has been set very high in spite the fact that we all recognize that we will never be able to replicate an epidemiological study in a laboratory setting, unless we recruit two million individuals for a chamber study! I think for quite a long time the scientific community has approach this issue with an unjustified naiveté and we ought to realize this soon. To my mind in spite the fact that toxicological studies have not produced coherent results as we would wish, we have more than enough evidence that there is something is going on. This is important because we were not able to make this statement in 1997. We ought to acknowledge the fact that a great progress has been made both in terms of using adequate animal/human models and particles/particle surrogates. In addition, one can argue that a great deal funding, expertise and state-of-the art methods have drawn upon to study biological mechanisms. Of course, we are not done and it is up to us to say whether the glass half full or half empty.

4) Finally, bio-aerosols got some attention. However, If the review took place earlier, I would have suggested that this information be distributed appropriately to the different chapters e.g. properties, exposure, toxicology and epidemiology. It may be too late at this point.

5) Finally, the chapter could benefit from being a little concise. There are many studies repeated and actually described several times. One could deliver the same information in 150 pages very easily.

Dr. Paul J. Lioy

CHAPTER 8 – December 2003 Draft of AIR QUALITY CRITERIA FOR PARTICULATE MATTER (EPA/600/P-99/002, bD)

Comments of Paul J. Lioy

General: The current Draft of PMCD Chapter 8 is an improvement over the previous version. The authors paid attention to many of the comments made by the Committee, and deserve credit for their work. The interpretation and summarization is very good for the many studies that have been conducted or reanalyzed since the 1996 Criteria Document. Even though there is large amount of variation in the types of studies, the metrics of exposure, and a continuing search for the best biological and/or other markers of exposure to relate to the responses attributed to PM or its size fractions, the Chapter provides sufficient information to describe the state of the science. I am pleased that within the text there has been in a concerted effort to clearly define the PM metrics (e.g. $PM_{2.5}$) that have been used in individual studies, and to identify those used to compare specific health outcomes. However, this approach needs to carry over to the summary of key findings section, especially within the list of salient conclusions. This point will be discussed below. I commend the authors on the way in which the GAM issue has been discussed in the chapter. The summary of GAM was both easy to read and understand. I think with minor changes Chapter 8 is ready for closure.

Specific Comments - requiring revision:

1. Pages 289 -295. The authors slip back in this section a little. There are a number salient conclusions that are associated with "PM" and not one or more specific classes, e.g. PM_{10}, $PM_{2.5}$. Please review each conclusion and determine whether or not there are truly about general "PM "or specific size fractions. For example, conclusions 5, 6, 8, 10, 17, 18, and 19. This is an important concern, since only one major conclusion, #3, actually discusses conclusions from studies associated with $PM_{2.5}$. The other conclusions do not specifically account for the results from specific $PM_{2.5}$ studies and analyses reported in the text. The issues surrounding PM are complex, the more exact the agency makes the discussion and conclusions the easier it is to interpret the strength of the evidence.

2. Section 8.46 seems to be buried in its current location – concentration – response relationships for ambient "PM." It should either go right before the summary or closer to the front of the document (probably the latter) to receive some attention from the reader.

3. Section 8.4.10.3 – Infant mortally the statements at the end of the section are confusing and should be dropped from the text. It should end with – we need more research.

4. In the section on Co-Pollutants (8.4.3) and in the salient conclusions section, the authors need to make the point that more information is needed on the potential health related

synergisms or antagonisms caused by the simultaneous presence of PM or individual PM size fractions with other air pollutants. This is a complex problem caused by a complex mixture of gases and particles. Many epidemiological studies reported in the Chapter are focusing on the multi-pollutant problem. Thus, the chapter needs to provide a firm and well focused discussion on the science being completed, or the hypotheses being tested by investigators, which is in addition to discussion on statistical analysis issues.

Dr. Mort Lippmann

REVIEW COMMENTS
Morton Lippmann

CHAPTER 7 – December 2003 Draft for AIR QUALITY CRITERIA FOR PARTICULATE MATTER (EPA/600/P-99/002, bD)

SUMMARY COMMENTS

This (December 2003) draft of Chapter 7 now comprehensively covers the published peer-reviewed literature on the effects of experiment-based exposures of animals and human volunteers to PM and mixtures of PM and gaseous toxicants that are most relevant to setting PM NAAQS. The addition of the Appendix on Rat-to-Human Dose Extrapolation is welcome, and it was well done. While this chapter could be improved by further editing to eliminate some unnecessary detail, it is now in suitable form for CASAC closure.

GENERAL COMMENTS

Section 7.3.4, up through 7.3.4.6, beginning on p. 7-61 and ending on page 7-70, is not "Toxicology", and is analogous to text in Chapter 3 on Sources of non-biological PM. While it is not recommended that it be moved or become a separate chapter at this late stage of production of the AGCD for PM, there should be some introduction to the organizational anomaly on p. 7-61, and a note about the nature of the text on bioaerosols back in Chapter 3. Similarly, the text beginning on p. 7-71, and extending to p. 7-76 on "Atmospheric Levels", is analogous to text on ambient levels of other PM components in Chapter 3.

The text beginning on line 13 of p. 7-76 and extending to line 26 of p. 7-78 is on epidemiology. Also, there are similar "non-toxicology" sections in Chapter 7 relating to fungi and endotoxins that extend to page 7-90.

Page-Specific Comments

page	line	comment
7-2	25	insert "ambient air" before "exposures"
7-3	4	add "or susceptibility" after "retention"
7-3	10	change "understanding" to "that can account for the"
7-5	8	insert "or particle component"
7-7	17	"MI" is not defined until line 12 on p. 7-8
7-21	9	clarify what is meant by "changes, while small, are clearly not consistent"
7-26	16	"Ottawa" was misspelled
7-54	21	insert "particle" before "clearance"
7-69	24	delete the first "in"
7-113	12,14	"coarse" is not synonomous with "PM_{10}"
7-136	27	change "Helen" to "Helens"
7-166	7	what is $\mu gcpSO_4^{2-}$"?
7A-5	5	insert "more nearly" before "symmetrically"
7A-7	18,19	move this sentence to line 8
7A-8	15	"Cassee" is misspelled
7A-14	2	insert "to" before "be", and "associated with" before "increased"
7A-14	3	change "provided" to "provides"
7A-14	10	insert "(e.g., cigarette smoke)" after "toxicants"

REVIEW COMMENTS
Morton Lippmann

CHAPTER 8 – December 2003 Draft for
AIR QUALITY CRITERIA FOR PARTICULATE MATTER (EPA/600/P-99/002, bD)

SUMMARY COMMENTS

This (December 2003) draft of Chapter 8 is a great improvement over the previous one. It is better organized and more dispassionate. Within the constraints imposed by the absence of data on critical unresolved issues, apparent conflicts in findings and conclusions in the peer reviewed literature, our limited knowledge of the biological basis for the health effects associated with exposures to ambient air PM and other pollutants, and variations of exposure within the members of the populations that have been studied, the authors of this chapter have made judicious selections of the papers to discuss, and have made reasonable interpretations of the data. While the chapter would benefit from further editing to reduce redundancies, it is now as complete and impartial as it needs to be, and ready for CASAC closure.

GENERAL COMMENTS

Section 8.2.3.1.2 (p. 8-81) introduces the semi-individual chronic exposure studies without informing the reader about the key characteristics of the populations and how they influence later interpretations of the findings concerning applicability to standard setting. This is especially important in relation to the ACS and Six-Cities cohorts because the provide key information informing the annual $PM_{2.5}$ NAAQS. It should be noted, in this section, that the Six-Cities cohort was pre-selected, by the investigators, to be a representative population, at least for the region of the country that was (is) heavily impacted by both coal combustion and motor vehicle effluents. By contrast, the ACS study cohort is drawn from a large pool of volunteers who happened to live in communities where several years of fine particle and/or sulfate ambient air concentration data were available. It is important to note that the ACS had a relatively small proportion of people with less than high school education (12% vs. 28% for Six-Cities) and, by

inference, better diets and access to good health care than an average U.S. population. To the extent that the mortality impact is lower in the better educated portion of the population, the mortality experience of the ACS cohort provides an underestimate for the U.S. population as a whole. By comparison, Section 8.2.3.2.3 (p. 8-99) on the AHSMOG cohort, and Section 8.2.3..2.4, on the EPRI veterans cohort (p. 8-103) do introduce the special attributes of these two other cohorts.

In Section 8.2.3.2.5 on the relationships among the four cohort's findings (p. 8-106 and in Table 8-11), there should be some discussion of the effects of the nature of the cohort selection on the differences in reported RRs.

In Section 8.2.3.6 on "Salient Points" from chronic PM mortality studies, there is no discussion whatsoever on the Pope et al. (2002) results for the ACS update study. Its findings on a significant $PM_{2.5}$-related excess of lung cancer and its update on current $PM_{2.5}$ levels and their implications to the interpretation of long-term exposures need to be discussed in this section.

Section 8.4 "Interpretive Assessment" starts out appropriately in terms of Section 8.4.1 "Introduction". Section 8.4.2 "GAM Issue and Reanalyses Studies" is a good summation, making appropriate use of summary figures. Unfortunately, the balance of the chapter has too many parts with too much detail, where the discussion is redundant with the information in the preceding Sections of the chapter. These parts should be greatly condensed and should present only the essential information. Figures 8-18 through 8-21 are good examples of such summarization. Other sections should also summarize the findings in new summary figures or by reference to summary figures in preceding sections.

Page-Specific Comments

page	line	comment
8-3	11	change "crusted" to "earth crustal"

8-3	21	change "is" to "are"
8-7	4	change "short" to "shortly"
8-50	16	change "COH" to "CoH"
8-90	8	change "eight" to "nine"
8-90	10	change "eight" to "seven"
8-96	8	change "eight" to "seven"
8-116	29	change "frame" to "frames"
8-119	15	delete "and"
8-127	24	a cross reference to Chapter 7 is needed here
8-138	13	a paper (Metzger et al.) that is "in press" violates the inclusion rule
8-142	11	what is the distinction between the two sets of data on "cardiac causes"?
8-153	1	change "An important" to "A potentially important"
8-155	24	insert "in" after "levels"
8-155	27	delete "intriguing"
8-156	8	change "is" to "are"
8-173	12	insert "to be" before "strongly"
8-174	4	the sentence is incomplete
8-197	30	the children did not move to other locations "as a group". They left their cohorts and were studied as individuals.
8-199	22	delete "studies that"
8-199	23	delete "combine the features of cross-sectional and"
8-199	24	delete "These studies include Peters et al. (1999b)"
8-199	26	insert "cross-sectional study of the children in the Gauderman et al. (2000, 2002) cohorts before "found"
8-199	31	insert "and sulfate" after "acidity"
8-216	4	change "well" to "widely"
8-224	28	change "follow" to "follows"

8-237	9	delete "well" and "inhalable"
8-237	10	delete "thoracic particles (indexed by PM_{15} or PM_{10}) and the" and "fraction of such"
8-237	12	delete "4-18% per 20 $\mu g/m^3$ $PM_{15/10}$ increment and"
8-237	13	add "The results for PM_{10}, TSP, and the fractions of these indices that excluded $PM_{2.5}$ were not consistently associated with cardiopulmonary or lung cancer mortality."
8-242	11	add ", O_3," after "PM_{10}"
8-242	27	change "15" to "16"
8-248	11	insert "4-year cohort" after "Gauderman"
8-248	12	insert "in children recruited in 4^{th} Grade that were" after "growth"
8-248	13	insert "in the cross-sectional study of the children at the time of their recruitment" after "levels"
8-248	15	insert "and sulfate" after "acidity"
8-248	18	change "Still insufficient data exists from these relatively limited studies" to "The data from these relatively limited studies are still insufficient"
8-248	25	change "selecting lags" to "lag selection"
8-249	1	change "day" to "days"
8-251	13	change "may" to "generally"
8-261	7	change "olde" to "older"
8-280	12	add "Also, most of the H^+ measurements were below the detection limit."
8-291	3	change "a" to "an average"
8-291	10	change "Brunekreef (1997)" to "life table calculations" (The 1.31 years cited above was not Brunekreef's calculation)

Dr. Joe Mauderly

Review of Chapter 7 of PM Criteria Document

Joe Mauderly

General Comments:

Body of Chapter

Overall, the chapter is improved, although it still needs a bit of minor editing. Most previous concerns have been addressed.

Attention to presenting exposures and doses for all studies cited in the text has improved, but the issue is still handled unevenly throughout the chapter. The authors should decide whether they will give exposure (or dose) information in the text, or whether that information will be limited to the tables. At present, information is given in text for nearly, but not quite, all of the studies cited in the text, but the completeness of the information given is variable. For inhalation exposures for example, the reader needs to know the exposure material, time, and concentration. There are still a few places where exposures are not described, and sometimes concentrations are given without times. Either present all the information necessary to place the results in context, or note that the reader is expected to get that information from the tables.

The addition of the material on "bioaerosols" is a big improvement. With all the evidence for the importance of PM-borne, bio-derived materials (not just PM wholly derived from biological sources) presented in the section, it's a mystery that the Agency had planned to disregard it. The section presents a dilemma, however, because it contains information on the nature of PM-borne biological material and exposures – issues that should be inserted into preceding chapters. Because the material is relatively well written, it seems that Staff and the Panel could agree that those paragraphs could be inserted into preceding chapters without having to review chapters on which we've already closed. If not, then keep it all here – better to have it here and a bit out of place than to delete it altogether. The section needs a table of health studies, in parallel with the tables presented for other topics.

The Summary section is a big improvement, and can be made acceptable with a bit of editing.

Appendix 7A

The inclusion of Appendix 7A is an appropriate step toward dealing with the dose extrapolation issue, as the Panel has repeatedly requested. Unfortunately, I find the Appendix to be confusing and of little value as presently developed. The bottom line of the Appendix is that virtually any high dose is OK for animal studies, which, while understandably serving the interests of including lots of high-dose studies in the CD with little discrimination, is not convincing. The particular examples presented don't engender confidence.

Comparing rat dose metrics after exposure to 2 μm PM to human dose metrics after exposure to a "busy road" size distribution of PM goes too far in terms of "comparing apples and oranges". Contrary to the impression given by the Appendix, rodents are often exposed to smaller PM and to PM having a "roadside" size distribution. The fact that 2 μm is "typical" of inhalation studies may be true for the ROFA literature, but the comparison doesn't pertain to the broader range of CAPs, ultrafine, DPM, or combustion emission studies. Moreover, the epidemiology literature is linked to $PM_{2.5}$ and PM_{10} at area air monitors, not to "roadside" size data. A simple, straightforward comparison of dose metrics between rats an humans exposed to PM having the same size distribution would be easy to do, and informative. Intended or not, the present comparison reeks of having been selected to justify high doses rather than to give an objective view of comparative doses.

The Utah Valley comparison really tips the scales! It goes something like this: The instilled human doses are justified as equivalent to 5 days of exposure, which in turn assumes that the PM was 1 μm, to be consistent with instillation at the 4th airway generation of humans. It is then assumed that the exposure concentration was 300 $\mu g/m^3$ and that 65% was $PM_{2.5}$, so the exposure is translated to 195 $\mu g/m^3$ for 7.5 days, presumably to 2.5 μm PM. (What this had to do with 1 μm PM instilled into the lingula isn't clear.) The dose was then translated to a single day's exposure to produce an air concentration of 1500 $\mu g/m^3$, before moving on to the rats. Perhaps the 24-hr period was related to the fact that the material was instilled instantaneously on one day. The rats were instilled (also instantaneously on one day) at various doses, and the lowest dose was selected for the comparison (250 μg, which apparently didn't cause significant effects, but effects that were "consistent" with effects from higher doses). A gobbledygook statement is then tossed in that rat doses were homologous to human responses. A 24-hr equivalent exposure concentration for the rat of 7600 $\mu g/m^3$ was then backed out, and victory was declared because this was only 25% higher than the "projected" human exposure concentration. The next paragraph starts out with the assurance that the rat dose was only 4-fold higher than the human dose. The foregoing may be a grossly inaccurate paraphrasing of the appendix, but the point is that I haven't a hint as to what it all means. It may be to my discredit, but the example neither educated nor reassured me.

Specific Comments:

Body of Chapter

P 7-3, L 10: It should be "—mechanisms of health—".

P 7-5, L 7-8: Although the primary effects might be outside the respiratory system, it's hard to see how the effects of any inhaled material could be "independent" of the respiratory system.

P 7-22, L 1: It should be noted that the dogs in this study were selected to have pre-existing cardiovascular disease.

P 7-22, L 7-21: Exposure concentrations?

P 7-22, L 27: Continuously for 1-3 days? The table says 3 hr.

P 7-23, L 6: Exposed for how long?

P 7-24, L 4-11: Exposed for how long?

P 7- 24, L 21: It should also be mentioned that there were no effects on respiratory function.

P 7-24, L 25-28: Which exposure levels caused effects? Were these effects seen at all exposure levels?

P 7- 25, L 16: Dose?

P 7- 26, L 4: "Concentrations" should be "doses".

P 7- 26, L 16: "Ottawa" is misspelled.

P 7-29, L 13-15: But this section focuses on respiratory, not cardiovascular, effects.

P 7-30, L 12-15: Why do we still have this reference, when it has been repeatedly noted that these results do not pertain to environmental PM?

P 7-30, L 25: Exposed for how long? No point in mentioning levels without the time.

P 7-40, L 24-25: We are given composition in mg/g and the total volume into which this was diluted, but that doesn't tell us the dose.

P 7-41: Doses for these studies?

P 7-43, L 24: The discussion here is not just about metals. This statement is incongruent with the rest of the paragraph.

P 7-44, L 12: It isn't really correct to call the neutrophil response an "adaptive" response. It may be a normal physiological response, a homeostatic response, a normal defensive response, etc., but unless you really mean that the response goes away with continued exposure, it's not really "adaptive".

P 7-45, L 6: Exposure concentration?

P 7-45, L 27: Exposure concentration?

P 7-46, L 11: Because "immunological changes" encompass so many different outcomes, a few more words should be given. For example, "amplification of respiratory tract allergic responses" would be more informative.

P 7-47, L 24: Here in one sentence, we see the words "trap" and "filter" used for the same thing. Be consistent.

P 7-49, L 4: Exposure concentration?

P 7-49, L 12: Exposed for how long?

P 7-54, L 26 and 29: Exposed how long?

P 7-56, L 1 and 12: Exposed how long?

P 7-61, L 7-8: Why mention <5um? Larger PM can penetrate into the deep lung – that's why we have a PM_{10} standard. Why state that bioaerosols pose little threat when the rest of the section goes on to catalogue numerous "threats"?

P 7-69, L 25: The sentence borders on the silly. As mentioned in previous reviews, the point is not at all whether bioaerosols can "account for " the effects of PM. No single PM component can "account for" PM effects. The point is whether bioaerosols can contribute to the effects of PM – which the rest of the section clearly indicates they can. Neither metals, organics, sulfates, nor any other component of PM can "account for" the effects of PM.

P 7-70, L 1-10: This paragraph, like the sentence on the previous page, is ridiculous and out of step with the rest of the section. Forget trying to set aside bioaerosols on the basis of their mass portion of PM – that's simply beside the point. Few, if any of the components of interest comprise a majority of PM mass.

P 7-73, L 30: Exposure parameters?

P 7-77, L 6-7: Here and elsewhere in the section, it would be better to also include common names for the bio-agents, if they have common names. Few, if any, readers would know what Poaceae, Betula, or Rumex plants were.

P 7-79, L 3: "Aribornes" should be "airborne".

P 7-79, L 23: It should be "—2 to 3-fold—"

P 7-84, table 7-7 title: "Ladened" should be "laden".

P 7-87, L 28: How were they exposed?

P 7-93, table 7-9: The abbreviations DPM and AM are not defined in the list at the end of the table, as are other abbreviations.

P 7-94, table 7-9, second citation: The in vitro exposure "concentrations" are given in $\mu g/m^3$, which is impossible unless the cells were exposed by aerosol.

P 7-95, table 7-9, second citation: The exposure is given in units of $\mu g/m^3$

P 7-108, L 30: The exposure is given in units of $\mu g/m^3$. Moreover, this dose is not listed in the table.

P 7-111, L 15, section on mutagenicity: There is literature on the mutagenicity of PM and PM-borne components from wood smoke, coal emissions, gasoline emissions, etc. No mention is made of those combustion PMs, but much mention is made of the mutagenicity of diesel PM. There is nothing wrong with discussing diesel. There is a lot wrong with not mentioning the others, and thus leaving a naïve reader to believe that DPM are unique in this respect.

P 7-113, L 11-23: The Hornberg et al. 1998 citation is troublesome, because the study is almost impossible to interpret in terms of relative toxicity. If one actually reads the paper, you find that they never give the dose given to the cells, or the information from which the reader can estimate the dose. Thus, one can't place the results in context. Because it is impossible to determine the dose, statements like the genotoxicity of 0.5 m^3 of air is meaningless. You could but the potential genotoxins in 0.5 m^3 air into a liter or a microliter. The final listing of the PM concentrations in air isn't helpful, because the paper presents no way to link those concentrations back to the cell results.

P 7-113, L 25: "Tracheo" should be "tracheal".

P 7-115, L 12-19: The term "fossil" should not be used for the fuel – whether or not the authors used it. The fuel was petroleum diesel. "Fossil" could also be solvent-refined coal fuel, Fischer-Tropsch gas-to-liquid fuel, or other fuels derived from fossil sources. Use the term "petroleum" if you want to distinguish it from biodiesel. The whole paragraph gives a misimpression of the situation. There are many kinds of "biodiesel" fuels, derived from numerous plant and animal triglyceride sources. Rapeseed oil-derived fuel is only one type. There is much more literature on the mutagenicity of various bio-derived diesel fuels than is suggested by this single reference. The term "green" is "political" term that is out of place here.

P 7-117, L 11-12: This statement is incorrect. The various fractions of diesel extracts are certainly not "too complex to characterize". They are not characterized routinely, because the analyses are complex, but that doesn't mean they are too complex to analyze – it just means it is seldom done. Of course this and many other organic samples contain a portion that has not been thoroughly resolved, but hundreds of compounds can be measured.

P 7-119,L 3-9: What was the exposure?

P 7-122, L 13: It should be "^{32}P" or "P-32".

P 7-163, L 7-8: This citation is not in the table. If it doesn't fit into the table, it doesn't fit into the text (and vice versa).

P 7-165, L 27-30: Exposed how long? Relative to what other combinations?

P 7-167, L 29 to 168, L 12: The "ambient exposure" studies are not useful references for this section. The exposures weren't characterized, and although they undoubtedly included PM, they do nothing to inform the PM discussion. They simply demonstrate that air pollution has effects. They certainly don't' fit in with the other studies in the section. The studies have value, but not for this document.

P 7-169, L 22: Size of PM?

P 7-169, L 27: The comparison depends on PM size. As noted under General Comments, these examples of rat-human extrapolation are poorly selected and confusing.

P 7-170, L 1-14: There are lots of problems with this comparison.

P 7-170, L 15: Herein lies the danger of the example just presented. A blanket statement whose impact and accuracy depends on PM size and other conditions. "The statement is not totally incorrect, but it's a gross over-simplification.

P 7-170, L 17-19: This is also a misleading, gross over-simplification. The impact of clearance depends on whether you are talking about single acute exposures or exposures over multiple days, weeks, or months. The fact that rats clear faster than humans can, but does not necessarily, support the use of high exposure concentrations and instillation dose.

P 7-172, 15-17: Metals are certainly not major contributors to toxicity of all combustion-related PM. How do you propose that metals are likely contributors to the effects described for DPM?

P 7-173, L 8: Is PM_{15} now within the definition of the coarse fraction?

P 7-173, L 31: There is also evidence (cited earlier in the chapter) that the black carbon fraction is also a contributor to the immune effects.

P 7-175, L 18: Despite the attempt of the appendix to justify any high dose, it seems a bit of a stretch to showcase this extreme example in the summary.

P 7-176, L 6-13: Especially in view of the time-sensitivity of these parameters, it seems that exposure time, and measurement time after exposure ought to be given.

P 7-179, L 9: It's inappropriate to use the term "green" diesel biofuel. "Green" is a political and marketing term, not a scientific term. Moreover, when you are talking about "biofuel", you need to specify the type. Biodiesel is made from everything from plant oils to used restaurant grease. Moreover, it makes a difference whether the fuel is used in neat form

or as a blend with petroleum diesel (which is usually the case). Using such jargon in naïve and uninformative.

P 7-179, L 11 and 13: Genotoxic" is misspelled.

P 7-179, L 24: You are totally overlooking the reported mutagenicity of other combustion PM. Giving the impression that DPM is the only specific PM type that is worthy of attention is misleading.

P 7- L 5-6: The principal limitation is not the fact that only a limited number of exposures can be conducted by a given laboratory in a given environment – in fact that is seldom the limitation. Concentrators can be moved, and operated most anywhere, most anytime. The principal issue limiting progress in using CAPs to disentangle composition-response relationships is the fact that the exposures are seldom characterized in sufficient detail. If enough emphasis is given to physical-chemical analyses, CAPs studies can be extremely helpful for this purpose.

P 7-182, L 17-28: Remember that the subject of the section is metals. The German cities gave different results, but was that related to metal content? The last two sentences have no apparent linkage to metals – they are motherhood statements that wander from the point of the section and are out of place here.

P 7-184, L 13: Diesel is only one of the sources of PM-borne organics. The interest in organics is not due to the fact that diesel PM is part of ambient PM, it's due to the fact that a substantial portion of the ambient PM is organic from various sources, and there is reason to believe that the organic has health importance.

P 7-184, L 19-20: Why is this statement about PTFE PM vs "fumes" included? That issue never had anything to do with environmental PM (as the principal investigator has repeatedly reminded the Agency). Moreover, "fume" is a term that is usually intended to encompass ultrafine PM; thus, talking about "fume" absorbed to PM doesn't make much sense.

P 7-185, L 12, section on bioaerosols: This section needs to be condensed to parallel the level of information contained in the preceding sections summarizing other issues.

P 7-188, L 23 to 7-189, L 2: As discussed in an earlier comment, the types of studies described in this paragraph don't speak directly to the issue of PM and co-pollutants. The only connection is that the air pollution at various sites was undoubtedly composed of both PM and non-PM components. One can't possibly tease out PM vs co-pollutant effects, or interactions between PM and co-pollutants from these studies. If you feel compelled to mention this kind of work, it can be summarized in a single sentence at the end of the next paragraph. I wouldn't mention it at all in this summary section.

P 7-189, L 13-29, section on susceptibility: This is not a good summary of the susceptibility issue and its attendant advances. The first paragraph conveys the notion that work on susceptibility is futile, and we have actually perhaps even taken steps backward. The

second paragraph talks only about exacerbation of immune responses, which is only one of many susceptibility issues that have been researched. The section should note that work in this area has increased, that some selected or induced "susceptibility" models have been shown to be more responsive than normals, list some of the predominant types (models) of susceptibility that have been studied, and then – only then- note that this is a difficult area, no "best" model or models have yet emerged, and the search for adequate models continues.

Appendix

P 7-A-5, table &A-2: The assertion that exposures of rats are "mostly to resuspended dusts" is misleading, if not untrue. It is true for ROFA, if one chooses to call ROFA "dust". It is not true for CAPS, or for DPM, or any combustion source emissions. Does MMD mean MMAD?

P 7A-7, L 25-29: The business about equilibrium burden pertains to continued uniform exposures. As the exposure concentration varies with time, as is certainly the case for a 60-yr old human, there would be continual shifts toward new "equilibria".

P 7A-7, L 30: Rats are frequently exposed to PM resuspended from bulk material, but they are also frequently exposed to other PMs.

P &A-8, L 18: Presumably, "multipass" should be "multipath".

P 7A-8, second paragraph: The whole business of comparing dose metrics in rats exposed at rest to 2 μm resuspended PM to humans working near a busy road is misleading at best and nonsensical at worst. The resuspension studies are not intended to mimic roadside exposures – by which selection and size distribution you are implicating vehicle emissions. Animal studies of vehicle emissions don't use resuspension of 2 μm particles. The epidemiological studies are based on area monitors, not roadside monitors, so your human exposure scenario doesn't match up well with PM epidemiology. The only conclusion a reader can draw is that you have used rat and human exposure scenarios selected to maximize your ability to claim that the extreme doses of resuspended PM are justified. The whole comparison is flawed from the beginning, and by making these selections, you undermine the credibility of the appendix and its intent. Present some comparisons using identical PM size distributions.

P 7A-10, table 7A-3: The value for rat FRC seems high. For example, you don't get FRCs in the 4 ml range in F344 rats until they are around 2 yrs old. The young adults used in most studies have FRCs closer to 3 ml. Of course, that's in anesthetized rats – it's unclear how that relates to conscious rats. It would be useful to give the source for the values used as constants in the calculations.

P 7A- 11, L 17: It's not clear whether you assumed daily exposure of 5 day/wk exposure.

P 7A-11, L 19-25: I, for one, can't follow these assumptions sufficiently well to judge them. After several readings, I still am not confident that I understand the strategy for accounting for both acute and historic exposures. An "experimental design" diagram might help, but I suspect that I wouldn't be convinced of the reasonableness of any set of assumptions that I can't follow in writing.

P 7A-11, L 26-27: One might accept the assumption that 50% of PM to which humans are exposed could be considered "soluble", but that assumption would not be valid for the types of 2 μm PM to which you say rats are "typically" exposed. Moreover, solubility is an imprecise term – some components dissociate from deposited PM in seconds to minutes, and others probably in hours to days. It is not clear whether that was considered, or how that was dealt with in the calculations.

P 7A-12, table 7A-6 footnote: Apparently, the "[a]" superscript in the headers is supposed to refer to the "[1]" indicator given for the footnote. Make them match.

P 7A-14, L 12-15: Using increased dose would only be valid if you believe that the human susceptibility is due to increased dose (as in increased deposition in COPD). If the human increased susceptibility is not due to increased dose, then jacking up the rat dose not comprise a valid model. It is far too common a misconception that a high dose in animals is justified because of interest in susceptible humans. That is only true if you are interested in humans that are made susceptible because they have higher doses (because of increased exposure or depositon, reduced clearance, greater access of putative components to target tissue, etc.) – not if their susceptibility is due to other conditions or mechanisms.

P 7A-14, L 24: I think it should be "instillation".

P 7A-14-17: Despite multiple readings, I am not sure I understand the assumptions and calculations used in the rat vs human "Utah Valley PM" comparison. What I can understand suggests that the shifting back and forth from inhalation to instillation and from doses to air concentrations is tantamount to a shell game. The comparison strategy doesn't make sense to me. No specific comments will be attempted.

P 7A-20, L 15: It should be "—have been—".

P 7A-21 – entire paragraph: The appendix and the comparisons selected for illustration appear slanted to reach this "bottom line". The use of high doses in animals to evaluate effects likely to occur in humans is sometimes valid and sometimes not. It depends on the situation and the dose (or concentration). The present conclusion suggests that any dose or concentration used in any animal study to date is OK, and the results can be "believed" in terms of their validity for hazard assessment, dose-response characterization, and studies of mechanisms and susceptibility – i.e., no dose is too high. I don't believe that. The appendix falls short of putting the issue into proper context.

Dr. Roger O. McClellan

Comments on Revised (December 2003) Chapter 7 – Toxicology of Particulate Matter in Humans and Laboratory Animals

and

Chapter 8 – Epidemiology of Human Health Effects Associated with Ambient Particulate Matter

In

Air Quality Criteria for Particulate Matter

by

Roger O. McClellan, DVM, DABVT, DABT
Consultant, Toxicology and Human
Health Risk Analysis
13701 Quaking Aspen Place NE
Albuquerque, NM 87111

February 9, 2004

A. CHAPTER 7 (Toxicology)

Summary

The revised (December 2003) chapter 7 – "Toxicology of Particulate Matter in Humans and Laboratory Animals" is not a scientifically adequate review and evaluation of the relevant scientific literature on the Toxicology of Particulate Matter as required to provide criteria for establishing the National Ambient Air Quality Standard for Particulate Matter (PM). The administrative decision to restrict the review to literature developed after preparation of the 1996 PM Criteria Document has resulted in a biased evaluation of the literature because highly relevant earlier literature was ignored. Moreover, the review and evaluation of recent literature is biased because of the heavy dependence on recent research conducted by the U.S.EPA on a very specific kind of PM, Residual Oil Fly Ash (ROFA).

The persistent effort to portray ROFA as having effects and operating via mechanisms that can be generally attributed to ambient PM throughout the U.S. is not well supported. To the contrary, consideration of the totality of literature available on particulate matter toxicology, including pre-1996 literature, indicates that PM, differing as to chemical composition, physical characteristics and size and source, varies markedly in its toxic potency. This is an important conclusion, unstated in Chapter 7, that suggests that a National Ambient Air Quality Standard based solely on size differentiated PM mass may not be appropriate and, moreover, related control strategies may be flawed and not yield anticipated public health benefits.

Introduction

These written preliminary comments reflect my initial assessment of the revised Chapter 7 (December 2003). They are based on my review of the revised chapter with regard to its scientific adequacy for providing criteria for establishing a National Ambient Air Quality Standard for PM

General Comments

1. The revised chapter 7 is seriously flawed as a result of the administrative decision to restrict the review to literature published after the preparation of the 1996 Criteria Document on PM was completed. Although this decision may have been well intended in restricting the amount of material the authors would be required to review, the truncated approach is not consistent with how scientific information is developed, evaluated and synthesized.

Science in any area does not move forward in a series of neat and orderly steps. Rather the acquisition of scientific information, even when subjected to some planning, moves in a somewhat random manner. New information sometimes advances hypotheses built on previous findings. In other cases, hypotheses are rejected. In other cases, totally new hypotheses are advanced and require testing. At any point in time any understanding of a particular subject matter topic represents a distillation and synthesis of all the previously acquired information. To restrict a review to a specific time period artificially "casts in stone" the state of knowledge at the beginning of the evaluation period.

In the case of PM, the time period constraint is especially inappropriate because a lot of knowledge about PM toxicology was developed pre-1995. Moreover, that knowledge was not especially well reviewed in the 1996 Criteria Document on PM. The brief reference to the contents of the 1996 document is useful but not sufficient to convey the robust nature of the information available pre-1996. During the February 3, 2004 teleconference, Dr. Les Grant recalled that at the request of CASAC, substantial material on PM toxicology was removed from the 1996 CD. Perhaps consideration should be given to including that material as an appendix in the 2004 PM CD or otherwise referencing it.

In general, the pre-1996 literature revealed that many different kinds of PM from different sources and of differing composition, had relatively low toxic potency. In some cases, materials such as coal-fired power plant fly ash, sulfur dioxide, sulfuric acid, titanium dioxide and carbon black had been evaluated in well-conducted long-term studies using inhalation exposure, the most relevant mode of exposure for evaluating the health effects of airborne PM. A few relevant references are Alarie *et al* (1970, 1972, 1973a, 1973b, and 1975), MacFarland *et al* (1971) and Raabe *et al* (1982). There are also numerous pre-1996 papers on specific aspects of the toxicity of PM.

Some of the early work related to coal combustion is reviewed in a document compiled and edited by Hobbs (1983). It includes an extensive list of references. An example is the Mumford and Lewtas (1982) from EPA noting much lower mutagenicity of conventional combustion fly ash compared to fluidized bed combustion fly ash. A large base of information, largely pre-1996, on secondary inorganic particles, principally sulfates and nitrates, was recently reviewed by Schlesinger and Cassee (2003). They conclude – "these particles have little

biological potency in normal humans or animals, or in the limited compromised animal models studied at environmentally relevant levels."

The conclusions drawn from the totality of the pre-1996 literature stands in stark contrast to the post-1996 literature reviewed in the revised Chapter 7. It is appropriate to ask why? The major difference I will discuss next is the introduction into the current chapter of a large number of studies conducted in the U.S.EPA laboratories with a specific kind of PM, ROFA.

2. The revised Chapter 7, by focusing on ROFA without considering literature on other PM, creates the impression that all of the effects and mechanisms observed in studies with ROFA are representative of what one would find with all ambient PM. Moreover, the document inappropriately creates the impression that all "combustion" or "combustion-related" particles are similar. This unfortunate lumping begins on page 7-3, lines 24 and 25 and is replayed throughout the chapter. The chapter repeatedly conveys the impression that ROFA is a typical combustion-related particulate matter. In some places, such as Table 7-1a, pg 7-11 to 7-14, the term "emission source PM," is inappropriately used as short-hand in a column describing the "Particles" and then ROFA appropriately used under the column labeled "cardiovascular effects." Perhaps this is just sloppiness on the part of the authors. An alternative view is that the authors are deliberately trying to characterize this specific kind of PM as being representative of all PM because it is perhaps the most toxic of the PM studied. Moreover, it is the specific kind of PM studied by the USEPA almost to the exclusion of other PM. The ROFA theme continues to be played in the Appendix to the chapter which focuses heavily on the ROFA example. In doing so, it neglects consideration of the issue of extrapolating from rats to humans for studies with other kinds of PM.

The ROFA equals "combustion-related PM" is even played out in the captions to tables such as Tables 7-1A and 7-1B where it appears that the only combustion-related PM studies included in the tables are those with ROFA.

My specific recommendation is that when effects/mechanisms are found, or are not found, with ROFA or any specific PM that care be taken to properly note the "test agent." When summary statements are made, care should be taken to avoid leaving the impression that the effect/mechanism has been found with all types of PM. Summary statements attributing

effects/mechanisms to PM in general should only be made when the observation has been substantiated in studies with several kinds of PM.

2. The chapter inappropriately moves to lump all concentrated PM (CAPs) as being equivalent. I suggest that tables, such as Table 7-16, pg 7-15 to 7-16, at least qualify each reference to CAPs with a geographical location such as Boston CAPs. Although it is now apparent that CAPs vary considerably in toxic potency, including day-to-day variation in the same city, the use of even the simple city descriptor will help serve as a reminder that all CAPs are not the same.

3. A major shortcoming of the chapter is the failure to relate the extent to which PM varies markedly in its toxic potency for causing adverse health effects. Hence, extreme caution should be exercised in attributing any effect or mechanism observed with one specific kind of PM, especially when it is ROFA, to all PM. It is important to critically examine the evidence.

Section 7.2: Cardiovascular Effects focuses on 30 studies reviewed in Tables 7-1A and 7-1B. Sixteen were conducted with ROFA and 5 with CAPs, usually without including a "comparison material." For studies in which a "comparison" PM was studied a frequent finding was "no cardiac effects seen with MSH" (MSH-Mt. St. Helen's volcanic ash) or "CB no effect" (CB-Carbon Black). These summary statements are sometimes accompanied by related text such as "The observed adverse effects ----- were much greater in the Ottawa- and ROFA-treated rats than in the Mount St. Helens" [ash, should be added for clarity] "treated rats." A careful reading of the text reveals other examples from the animal toxicology literature showing differences among different kinds of PM.

The findings are not restricted to the animal toxicology literature. On pg 7-24, the work of Frampton (2001), as noted in the chapter, studying human subjects exposed to carbon black is described. The conclusion – "Preliminary findings indicated no particle-related symptoms." Indeed, the statement would be more accurate considering the numerous health markers studied if the word "health related changes" were used instead of "symptoms."

In view of the foregoing, I would have expected the cardiovascular section (7.2) to conclude with a statement such as "In the studies conducted to date changes in cardiovascular disease related parameters have not been found in a consistent manner in the toxicological studies with controlled exposures conducted to different kinds of PM. The most consistent cardiovascular effects have been found with ROFA, a rather unique type of PM with a high

transition metal content. A limited number of studies with other kinds of PM have not demonstrated similar effects. Unfortunately, no controlled exposure studies have been done with PM rich in sulfates or nitrates, two common and abundant PM constituents in many parts of the U.S. It is apparent that future research should focus on determining the extent to which the observations with ROFA can be generalized to other PM."

In Section 7.3 on Respiratory Effects, the dominating influence of the literature on ROFA continues to dominate the discussion. In Table 7-4, 48 studies are reviewed of which 25 used ROFA. In a few cases, the ROFA studies included other kinds of PM. Seven studies used CAPs. It is interesting that 3 of the 7 CAPs studies were summarized as having NO responses or changes. A review of the table indicates the studies reviewed are certainly not representative of ambient PM across the U.S. Nonetheless, on pg 7-43, one finds the extraordinary summary statement – "The fact that instillation of ambient PM collected from different geographical areas and from a variety of emission sources consistently caused pulmonary inflammation and injury tends to corroborate epidemiological studies that report increased PM-associated respiratory effects in populations living in many different geographical areas and climates." I view this as a very selective and biased evaluation of the literature, bias that is even more strikingly apparent when pre-1996 literature is considered.

The sub-section on diesel particulate matter also presents a very biased consideration of the literature. The EPA Diesel Health Assessment Document (EPA, 2002) that was developed over the course of more than a decade provides a rich source of information on the effects of diesel exhaust. In particular, it includes detailed reports of chronic multiple exposure level studies, conducted with the most relevant mode of exposure – inhalation. The contents of that authoritative review are briefly summarized, without reference to exposure level or duration in the current chapter. It then proceeds to focus on recent studies conducted in some cases with poorly characterized exposures or non-physiological modes of administration of diesel exhaust particles or extracts.

The section (7.3.1.3) entitled "Complex Combustion-Related Particles" is grossly mis-titled; it should be correctly titled "Residual Oil Fly Ash Particles." This is a rich data set. Indeed, it may be sufficient for the EPA to use in categorizing ROFA as a hazardous air pollutant, it would not qualify as a criteria pollutant because of its limited geographic distribution.

The section (7.3.2) on "Acid Aerosols" appropriately starts with the statement – "The Studies summarized in the 1996 PM AQCD illustrate that aqueous acidic aerosols have minimal effects on symptoms and mechanical lung function in young healthy adult volunteers at concentrations as high as 1000 $\mu g/m^3$." The section continues with an expanded discussion of human studies and brief references to several recent studies conducted in laboratory animals. One of these is a study in which dogs were exposed to 1.5 mg/m^3 of acid aerosol for 16.5 hours per day for 13 months without observing any respiratory effects. The next sentence is rather curious – "Thus, recent studies provide little additional evidence demonstrating that relevant concentrations of aqueous acid aerosols contribute to acute respiratory effects of ambient PM." I guess the authors just could not bring themselves to make an explicit statement saying the evidence is not there for an effect of sulfate aerosols on the respiratory system. Instead, they elected to conclude the sub-section on acid aerosols and respiratory effects with a statement on the need for studies of the effects of acid aerosols on the cardiovascular system. I concur – the paragraph needs to be moved to the cardiovascular section of the chapter.

A strong concluding statement for an absence of respiratory effects from sulfate aerosols should be supported by referencing the excellent review of Schlesinger and Cassee (2003) and the early work of Alarie and MacFarland and colleagues who conducted long-term inhalation exposure studies of acid aerosols and fly ash in monkeys. The remainder of the section provides a brief review of metals and an extensive discussion of bioaerosols.

The section on respiratory effects ends abruptly without a summary. Let me suggest one. "The respiratory effects of different kinds of PM have been extensively studied for more than 30 years using a wide range of techniques and with exposure durations ranging from brief periods of time to months. The most extensively studied materials have been sulfates and acid aerosols formed as secondary pollutants in the atmosphere. Fly ash from coal-fired power plants has been less extensively studied. The toxicological data available today do not provide a basis for incriminating these PM constituents as having substantial respiratory effects at ambient levels of exposure. Recently, ROFA, a very specific kind of PM, has been studied extensively and found to produce a range of respiratory effects. There is evidence for the transition metal components of ROFA having a mediating role in producing injury. There is a critical need for the systematic conduct of studies of the potential respiratory effects of major components of PM from different regions of the U.S. The stimulus for such studies is recognition that PM of

different composition and from different sources varies markedly in its potency for producing respiratory effects."

In Section 7.4 (Particulate Matter Pathophysiology and Toxicity: In Vitro Exposures), as the title conveys involved review of recent in vitro studies. Fifty-three studies are listed in Table 7-9 including 19 that studied ROFA. As in earlier sections there is a bias toward characterizing ROFA as a proto-typical PM whose effects and mechanisms can also be readily attributed to PM of different composition and from other sources.

4. In view of the dominant role of the ROFA studies in Chapter 7, it may be useful early in the chapter to have a graph and/or table comparing key chemical and physical characteristics of ROFA with those of several ambient PM samples, perhaps one from the eastern U.S., one from the western U.S. and one from Los Angeles.

5. Some improvement is noted in the description of many studies with regard to the mode of exposure, the quantity in the air or in the administered media, etc. However, for other studies this information is missing. For many studies, there is no indication of the exposure duration or observation period.

6. I suggest the section on bioaerosols be summarized in 1-2 pages and the bulk of the review of bioaerosols be placed in an appendix. This information is interesting. By and large, it is only relevant to the setting of the PM NAAQS to the extent it adds to the heterogenicity of responses based on mass measurements.

7. The section on mutagenicity needs to be re-written to reflect the available literature. The present version is excessively oriented to recent literature on mutagenicity of diesel exhaust and particle extracts.

8. The Appendix requires substantial revision. As a starting point the model being used and its origins should be briefly described. In doing so, it is important to note that many aspects of the model for both rats and humans have not been independently validated. Hence, it is unknown for some of the output values the extent to which they adequately predict what would be observed in laboratory studies or in the "real world."

One way to test the validity of the model applied to the rat would be to determine the agreement between model predictions and "measured" lung burdens of carbonaceous material in rats exposed to well-characterized diesel exhaust for two years at three different exposure concentrations (Wolff *et al*, 1987). The Wolff *et al* (1987) data were not used to

develop the model so the data set can appropriately be used to "test" the model. The lung burden measurements extend from 0.5 to 24 months of exposure.

9. Major changes are needed in Chapter 7, perhaps by incorporating key references to pre-1996 findings, to provide an adequate basis for discussion of toxicological findings in Chapter 9, the Integrative Summary.

Specific Comments

Pg 7-11, Table 7-1a: For first entry change "Emission Source PM" to ROFA. There is no need to be misleading when the specific emission source is known. In my opinion, the term – "emission source PM" is so general it has no meaning. Emission PM from vehicles fueled with gasoline, diesel, or natural gas, oil-fired power plants, coal-fired power plants, petroleum refinery, battery recycling plant and the list could go on.

Pg 7-11, Table 7-1a: The title of the table is misleading, the only "combustion matter-related particulate matter" studies summarized in the table use ROFA.

Pg 7-15, Table 7-16: Again the title is misleading. Most of the combustion-related particulate matter studies involve ROFA. A single study involved diesel exhaust PM.

Pg 7-16, Kodavanti et al, 2003: Is oil-combustion derived emission PM (EPM) a code word for ROFA. If so, why not say ROFA.

P 7-25, line 22: If ROFA is being used say ROFA. If it is something different from ROFA, then explain.

Pg 7-29, line 9: Appendix C to Chapter 3 says that organic compounds comprise 10 to 70% of dry PM, here 20 to 60% is used. The same value should be used for consistency.

Pg 7-33 and 7-40, Costa and Dreher (1997): Provide more information on the comparative toxicity of coal fly ash versus ROFA, DOFA and ambient PM.

Pg 7-38, Table 7-3a: Again, the title is somewhat misleading. Most of the combustion-related particulate matter is ROFA. Only in a few of the studies used PM from other combustion sources.

Pg 7-38: The use of the term – surrogate particulate matter is rather curious. I think all of the studies actually involved particulate matter so what does the "surrogate" modifier mean?

Pg 7-179, lines 20-25: The studies by Driscoll *et al* (1996, 1997), as noted in the chapter, are misrepresented. As I recall, there is a related paper by Oberdorster *et al* that does an

excellent job of summarizing these classic studies on the indirect or secondary genotoxic effect of carbon black mediated via particle overload and persistent inflammation.

B. CHAPTER 8 (Epidemiology)

General Comments

A number of improvements have been made in the main text of the Chapter in response to suggestions and criticisms of the prior draft by CASAC and the public. However, I remain concerned that a number of the comments, particularly of the public, have not been adequately addressed. I suggest that all of the previous comments as well as comments on this draft be very carefully reviewed by EPA staff. I have several concerns with the present draft as I will relate below:

1. The conclusions starting on pg 8-289 do not always appear to reflect the changes made in the primary text. Indeed, despite the statement "it is not possible to assign any absolute measure of certainty to conclusions based on the epidemiology studies discussed in this chapter" the conclusion goes on to convey, with biases, a much higher degree of certainty on the findings than is warranted.

2. The chapter repeatedly uses the term, PM, in an excessively vague and inclusive manner. The authors have inadvertently used the term, PM, in a manner that creates a "halo effect" in which findings with one PM indicator appear to be applicable to other PM indicators. I suggest the phrase, PM, be used sparingly and, whenever possible, the specific indicator (PM_{10}, $PM_{10-2.5}$, $PM_{2.5}$, etc.) be used.

3. The authors have over-stated the homogenicity, and under-stated the heterogenicity, of effects for all the PM indicators. The authors seem to be almost embarrassed to acknowledge heterogenicity (see pg 8-289, line 13). Perhaps they should simply acknowledge that in some studies and in some cities there is no apparent PM-associated effect for the indicator and endpoints studied. I am at a loss to understand how the authors can view 4- to 8-fold differences in effect size estimates as reflecting considerable coherence.

4. The authors mis-state the evidence for $PM_{10-2.5}$ effects (pg 8-290, line 15) and rely excessively on studies in Chile and Mexico. In this same section there is a need to be much more explicit as to the rationale for arguing for a $PM_{10-2.5}$ effect due to wood burning from studies in the western U.S. based on PM_{10}.

5. In the main text and in the conclusion section the "back of the envelope" life table calculations of Brunekreef (1997) are given excessive weight. I suggest that conclusion 6 be removed or toned down. Inclusion of the reference to the infant mortality studies is probably not appropriate in view of their weaknesses.

6. I applaud the authors' cautionary statement on pg 8-293 (line 23) that it is "inadvisable to pool epidemiology studies." I would prefer that the authors continue and caution against using concentration-response coefficients to calculate morbidity and mortality estimates for cities and time periods other than that of the study. The main text and conclusions need to explicitly acknowledge the difficulty of "testing" for a lack of linearity or a threshold.

7. The authors appear to have difficulty on pgs 8-293 and 8-294 in acknowledging that it is already apparent that certain classes of ambient particles are distinctly less toxic than others. The authors use the phrase – "may be." The authors apparently cannot bear to acknowledge that certain classes of PM at certain levels of exposure may not produce PM-associated health effects and, thus, no mechanism is operative. Rather, the authors appear to strain to explain how an absence of effects could be turned into effects (pg 8-294, line 25).

8. The conclusions should more adequately recognize the statistical weaknesses inherent in the time-series studies attempts to tease out a very small signal attributed to one or more PM indicators. I refer specifically to the comments offered by Switzer, Moogavkar and Smith in these proceedings and the papers by Koop and Tole and Humley and Sheppard and the report of the Health Effects Institute Panel.

In preparing Chapter 9, the Integrative Summary, I urge the EPA authors to avoid using the present Chapter 8 as a basis for the summary and, instead, carefully review the body of the text of Chapter 8. I urge that the epidemiology section of Chapter 9 provide a full exposition of the current knowledge of the health effects of each indicator, namely PM_{10}, $PM_{10-2.5}$ and $PM_{2.5}$ giving appropriate weight to studies of varied statistical significant from negative to positive. I am confident that when this is done the substantial heterogenicity of effects estimates will be apparent including the impact of other pollutants and key variables such as weather. An adequate exposition of heterogenicity in the epidemiological findings links well to the substantial heterogenicity of toxicological potency observed for different kinds of PM.

References

Alarie, Y., Ulrich, C.E., Busey, W.M. et al. (1970) Long-term continuous exposure of guinea pigs to sulfur dioxide. Arch. Environ. Health 21: 769-777.

Alarie, Y., Ulrich, C.E., Busey, W.M., ete al. (1972) Long-term continuous exposure to sulfur dioxide in cynomolgus monkeys. Arch. Environ. Health 24: 115-128.

Alarie, Y., C.E. Busey, Krumm, A.A., et al. (1973) Long-term continuous exposure to sulfur acid mist in cynomolgus monkeys and guinea pigs. Arch. Environ. Health 27: 16-24.

Alarie, Y., Kantz, R.J. II, Ulrich, C.E., et al. (1973) Long-term continuous exposure to sulfur dioxide and fly ash mixtures in cynomolgus monkeys and guinea pigs. Arch. Environ. Health 27: 252-253.

Alarie, Y.C., Krumm, A.A., Busey, W.M., Ulrich, C.E., Kantz, R.J., II. (1975) Long-term exposure to sulfur dioxide, sulfuric acid mist, fly ash, and their mixtures: results of studies in monkeys and guinea pigs. Arch. Environ. Health 30: 254-262.

Hobbs, C.H. (1983) Status of Research on Physical, Chemical and Biological Characterization of Particulate and organic Emissions from Conventional and Fluidized-Bed Combustion of Coal: 1976 to present. DOE/ER-1062.

MacFarland, H.N., Ulrich, C.E., Martin, A., Krumm, A., Busey, W.M., Alarie, Y. (1971) Chronic exposure of Cynamolgus monkeys to fly ash. In: Walton, W.H. ed., Inhaled Particles III. Surrey, England, Unwin Bros. Ltd., 1971. Vol. 1, pp 313-326.

Mumford, J.L. and Lewtas, J. (1982) Mutagenicity and cytotoxicity of coal fly ash from fluidized-bed and conventional combustion. J. of Toxicology and Environmental Health 10: 565-586.

Raabe, O.G., Tyler, W.S., Last, J.A., Schwartz, L.W., Lollini, L.O., Fisher, G.L., Wilson, F.D., Dungworth, D.L. (1982) Studies of the chronic inhalation of coal fly ash by rats. Ann. Occup. Hyg. 26(1-4): 189-211.

Schlesinger, R.B., Cassee, F. (2003) Atmospheric secondary in organic particulate matter: the toxicological perspective as a basis for health effects risk assessment. Inhal. Toxicol. 15: 197-235.

Wolff, R.K., Henderson, R.F., Snipes, M.B., Griffith, W.C., Mauderly, J.L., Cuddihy, R.G., McClellan, R.O. (1987) Alterations in particle accumulation and clearance in lungs of rats chronically exposed to diesel exhaust. Fund. Appl. Toxicol. 9: 154-166.

Dr. Günter Oberdörster

REVIEW OF CHAPTER 7 – PM CRITERIA DOCUMENT (G. Oberdörster)

The organization and text of this chapter are significantly improved compared to the previous version. The following summarizes questions/suggestions to consider for the final version. The Appendix 7A, Dosimetry/Extrapolation, requires some major rewriting.

Page 7-2, line 1: Add "mouth only" to the exposure conditions (reflecting controlled human exposure studies).

Line 2: add "intranasal instillation" after "intratracheal"

Line 11: delete the word "relatively"

Line 18: add after "doses" the words "deposited in the respiratory tract"

Lines 29-31: the appendix 7A studies are based on an invalid comparison which needs to be redone and the sentence be changed accordingly here.

Page 7-5, line 14: It sounds as if it is a fact that PM elicits vasoconstriction; I assume though that this is a hypothesis and it should be added by what mechanism, e.g., release of endothelin.

Page 7-8, line 9: I think it should be the other way around, i.e., the inflammatory response causing the release of C reactive protein and cytokines.

Page 7-10, lines 3-8: Are there any results to support this hypothesis? Or, what is the basis for it? I assume it is based on the Veronesi et al. studies, add reference.

Page 7-11: In this table for instillation studies, the "Mass Concentration" in the column heading should be replaced by "Dose"; and for "Exposure Duration" I suggest to label this column "Time Post-Exposure". The exposure technique for some studies is labeled just as "instillation" and in other studies as "intratracheal instillation". I assume almost all of these are intratracheal, so could all be labeled as "i.t. instillation". The last two studies in this table used "intrapharyngeal instillation", does this refer to the "oropharyngeal aspiration" technique, or is it really an instillation?

Page 7-15: In this table on inhalation studies, I suggest to replace the column heading "mass concentration" with "exposure concentration".

Page 7-17, line 6: What are listed here are effects and not mechanisms, please change the term mechanism.

Lines 8-9: I suggest in this sentence to replace "as" with a comma, and to delete "it induces" and add after "hypertrophy" the word "occurs".

Page 7-18, line 29: Studies by Watkinson et al. are listed here using a model of keeping rats in the cold: What human condition should this mimic with respect to PM exposures?

Page 7-19, lines 5-6: I am not sure how mechanisms can be consistent with the epidemiology? Effects may be consistent.

Lines 15-16: The use of instilled doses in order to determine inhaled concentrations (which then necessarily will be high) is a bit unusual, normally instilled doses should be based on inhalation.

Page 7-23, lines 12-21: The study by Nadziejko et al. is not listed in the tables to this section, although this study is extensively used in the Introduction to the Chapter.

Page 7-24, line 6: The high exposure concentration of 48 mg/m3 in the Ottawa dust study is given here; it would be helpful to also include the high MMAD of the aerosol in this study (around 4 or 5 μm) as an explanatory note.

Page 7-26, lines 1-10: The study by Nemmar et al. is reviewed here, however, the authors of this text mixed up intratracheal instillation with intravenous injection of the ultrafine particles in this study. Line 2 should be intravenous administration, and all of the doses should be μg/kg, not mg/kg. The results of the intravenous injection study start on line 1 and end with line 7, "body weight." Only the following lines refer to the intratracheal instillation study. In line 10, change "properties" to "charge".

Line 25: Include after "concentrations" the term "/doses"

Page 7-28, line 17: Misspelling - instillation

Page 7-32: Replace "concentration in:" with "dose" and change "exposure duration" to "time post-exposure".

Page 7-38: The study by Creutzenberg et al. is not a study designed as a surrogate PM study, rather it is a chronic particle overload study with poorly soluble low toxicity particles at high concentrations.

Page 7-41, line 21: Delete "but".

Page 7-48, lines 9 and ff: It needs to be mentioned here that almost all of these studies were done only with DE or DPM, no comparison was attempted with other PM; that means that the specificity of DPM is not proven by these studies; in fact, other studies where a comparison particle was used showed that these are as effective causing immune effects or even more so than DPM.

Page 7-51, line 13: It would be helpful to also express soluble metal compounds in terms of mass rather than μmoles, for easier comparison with the solid particle doses.

Page 7-59: The same comment as for the previous tables listing instillation studies, replace "concentration" and "exposure duration", respectively.

Page 7-77, lines 26-31: A few more details on this study in terms of doses administered and whether it was done by instillation or inhalation would be helpful.

Page 7-92, line 7: In this introductory section on in vitro studies, I suggest to add some other general statements about the design of in vitro studies such as: to perform them in a dose-response fashion; to express doses on a per cell basis rather than concentration per cm2 or concentration per mL: expressing dose per numbers of cells in the culture makes it easier to compare different studies with each other, (keeping in mind that we are dealing with averages per cell); to use comparison particles, i.e., positive or negative control particles or both; for example, rather than, saying "PM-x increases TNF□ 10-fold – which probably does any other PM as well - it would be much more helpful to express this relative to a positive or negative control particle; also, there should be awareness of the dosemetric, i.e., particle mass vs. particle number vs. particle surface area. I think such conceptual introductory remarks would be useful before going into describing individual in vitro studies.

Page 7-93: I wonder if the data in the column labeled "concentration" could be expressed as dose per cell? This may be possible only in very few cases.

Page 7-112, table on mutagenic/carcinogenic effects: The studies listed here are done with PM extract, and it would be useful for the reader to know the amount of particles from which it was extracted, and not only the extracted amount per se.

Page 7-135, line 27: Here and on the following page, the doses of ROFA and other PM should be given when reporting on the effect of PM on sensory nerves, (page 7-136, lines 20 and 29).

Page 7-137, line 3: This summarizing statement indicates that a plausible neurogenic basis is demonstrated by these studies. However, in order to agree with this and understand the plausibility it would be helpful to know the doses that had been used so one can put these in relation to doses received by inhalation exposures of the ambient PM (see previous comment).

Page 7-147, line 16 and ff: The statement here that SH rats were more sensitive than WKY rats with respect to vascular leakage appears to be incorrect: according to the results of the paper by Kodavanti et al. the BAL protein increase was actually larger in the WKY rats compared to the SH rats, although the absolute levels were higher in the SH rats, as were baseline levels.

Page 7-151, line 23 to Pages 7-153, lines 10 and Page 7-154, line 21: These studies with DPM showing adjuvant and other immunological effects are not necessarily DPM-specific since where no control PM was used as comparison. In fact, other studies listed in this same section show that all particles can exert an adjuvant effect on the immune response and that such response may be even greater with carbon black particles than with DPM.

Page 7-154, line 24 and 25: This statement is based on the above studies with DPM, and a caveat that any ambient PM may do the same thing would be appropriate here, and not just a DPM-specific effect.

Page 7-157, line 7 and 8: When comparing effects of leachate of ROFA with high concentrations of ambient PM, it would be helpful to include the amount of ROFA that was used to obtain the leachate aerosol (see previous comment regarding leachate concentrations in tables).

Page 7-163, lines 9-30: The study by Brook et al. with CAPs and ozone in human subjects is described here, but it is not clear as to whether another study with CAPs plus other gases was done by these authors at the same time. I do not recall that these other studies with co-exposures to CO, NOx, SO2 have been published in the same paper. How was the comparison of the PM + ozone study with the PM + other gases study done? Please clarify.

The interpretative summary of PM toxicology has been improved, although some parts are still only summarizing findings of Chapter 7. The beginning of this section starts with summarizing the dosimetry calculations of Appendix 7A. As is discussed there the approach taken there for comparing rats exposed to resuspended PM with humans exposed to ambient PM is not really valid, the model predictions need to be redone in the Appendix and the new results included here in this section. For example, on Page 7-169 lower part, to 7-170, upper part, the values need to be changed; also it is not clear to me as to whether the comparison to a human 24 hr. exposure is really based on humans breathing 40 L/min for 24 hrs., a very unrealistic scenario. I expect that based on the outcome of new model calculations, using a more realistic comparison between the two species, there will be several changes in this part of section 7.7. On the other hand, the general conclusion on page 7-170, lines 15-20, will remain that higher PM concentration exposures in rats are needed to make them equivalent to the human. But a caveat should be added that this does not mean that these concentrations are higher by factors of 10 or 100-fold.

Page 7-171, line 31: The same comment applies here, does an active person over a 24 hr. period mean a minute ventilation of 40 L/min over the whole time?

Page 7-175, line 1: It is indeed very plausible that instilled ROFA causes severe hypoxemia, the question is will ROFA cause this also at inhaled relevant concentrations. This question should be raised here as well.

Line 24: The decimal point in 0.34 is misplaced.

Page 7-179, lines 20-25: The studies by Driscoll (name misspelled) et al. showing increased HPRT mutations should not be viewed as showing primary genotoxicity, but the mutations are due to a secondary genotoxic effect caused by persistent pulmonary inflammation due to lung overloading. This ought to be made clear here.

Page 7-183, lines 19-24: The issue of DPM having adjuvant effects has been addressed before, and the statement that "it is not known whether adjuvant activity of diesel PM is unique or whether other combustion particles have similar effects" is not true since on page 7-151 and 7-152 of this Chapter studies are described with diesel, carbon black and silica, all having adjuvant effects, with carbon black having even greater effects than diesel. Also, at the recent PM Colloquium in 2003 in Pittsburgh, studies by Steerenberg (comparing DPM with road dust and

other particles) showed clearly that the other PM materials have potentially even greater adjuvant activity compared to DPM.

Page 7-189, lines 6-7: As mentioned before, the Brook et al. study does not discern a PM from an ozone effect, so we cannot say much about the combined effect when we don't know what the single components do.

At the end of this paragraph, additional studies with PM of different types in combination with ozone could be added, such as studies by Vincent et al., Kleinman et al., and Elder et al., all of which showed that the combination with ozone increases PM effects; so there is some evidence that PM in combination with an ambient oxidant gaseous pollutant increases effects.

Appendix 7A – Rat to human dose extrapolation

This section contains an extensive discussion of the possibilities to extrapolate and model results from animal studies to the human conditional although the main examples selected are interesting, they are not quite relevant for the goal to compare rat and human dosimetry under the exact same exposure conditions of PM. This section requires some revisions as discussed below; several other comments need to be addressed as well.

Table on page 7A-3: The table as shown is a bit confusing since it could be misread as consisting of three rows, one each for the thoracic, the tracheobronchial, and the alveolar region. I think it would be less confusing to turn the table around by listing the different dosemetrics horizontally on the left-hand side of the table followed in each row with the respective qualifiers. It would be helpful to define the thoracic region as meaning the total lower respiratory tract. Under the category respiratory region --- the nasal area should be added. Under PM indicators, "volume" should be added. Within the category "normalizing parameters", lung weight and nasal surface area should be added, and also surface area per region as well as surface area per generation of the airways; also, add to per alveolus or per macrophage also "per target cell".

Page 7A-3, line 12: Instead of "rat dose" state "dose per rat".

Line 14: Regarding the statement "it is not possible to be certain which combination would be most relevant" - one could certainly list some general concepts: for example, if we are dealing with soluble PM, then the mass is most likely the best dosemetric; on the other hand if we are dealing with insoluble PM, the particle surface area or particle number would be appropriate; if epithelial cells are the target, the tracheobronchial or alveolar surface area would be most likely the normalizing parameter; if the interstitium is the target, then the lung mass or weight would be the best parameters. I suggest to add these general concepts regarding the different usage of dosemetrics here.

Page 7A-4, equation in line 3: This equation is for the deposited dose only, one could also add an adjustment for different retention between rats and humans.

Line 5: These dosemetric adjustments are purely based on dosimetry, which is OK, but one could consider to include a statement here with respect to risk assessment. Generally, dosemetric adjustments from animal to humans still requires some additional

adjustment expressed as an uncertainty factor, which often is reduced from a factor of 10 to 3 when using the dosimetry adjustment.

Page 7A-5, table 2: The last section in the rat column on PM size distribution states that exposures are mostly to resuspended dust. This is not true as far as PM research is concerned; in fact, there are only a few studies that used resuspended dust, for example, the study by Vincent et al. with Ottawa dust with a really large MMAD. Otherwise, PM inhalation studies were mostly done with CAPs, ambient particles or with laboratory-generated surrogate particles with size distribution not different from the ambient ones.

Line 8: Since the rats don't have respiratory bronchioles, there is also no equivalent for this, terminal bronchioles immediately transit to alveolar sacs. The term transition zone maybe misleading, it is simply the BAD-junction.

Page 7A-6: The figure legend should include also the particle size, i.e., 2 μm with a GSD of 2. Also in the text to this figure, it would be useful to say something about deposition per unit surface area, comparing humans and rats, not just the fractional deposition.

Page 7A-7, line 1: After poorly soluble, I suggest to add "fine and coarse".

Line 3: Change "clearance halftimes" to "retention halftimes". The same applies to Line 5. Also in line 3, give reference for TB clearance rates being x-fold faster in rats than in humans.

Line 6: I suggest to replace "on the order of months" with "60 to 80 days" and add after "but": "up to two years".

Lines 9-10: The statement "because of the large fraction of particles removed in the nose of the rat" implies that in humans less particles are removed, which is not true for all particle sizes, e.g., ultrafines and nasal removal is pretty much the same in rats and humans.

Line 31, and Page 7A-8, line 1: The statement that rats are frequently experimentally exposed to resuspended particles does not apply for PM research, as mentioned above, and this should be changed here; yes, there are some studies with resuspended particles, but only a very few use that approach (Vincent et al.; perhaps some of the EPA studies). Thus, the MMAD of the resuspended particle size distribution should be changed here as well as in the subsequently used example when comparing rat and human exposures and dosimetry. Both species should be modeled as being exposed to the same particle size distribution.

Page 7A-8, line 20 and 28 (and throughout other sections of this document): All the predictions related to the rat studies modeled with resuspended PM should be changed because that is not typical for experimental studies with PM in rodents.

Page 7A-10, table 5: The lung mass of a rat is given here as 4.5 g which is extremely high; this rat would have a much greater tidal volume as is used in the Yeh and Schum model which is for a 330 g rat. At that body weight, lung weight is around 1.5 g.

Page 7A-11: as commented above, the comparison between rat and human doses received by the lung is based on the resuspended dust particle size distribution for the rat, a much more relevant comparison would be to use the same ambient particle size distribution for both rats and humans rather than the artificial resuspended dust.

Page 7A-12: It should be stressed in the text that these results are for humans at moderate exercise vs. rats at resting conditions. Which retention halftimes were used for humans and rats for TB and A region? Emphasize that retained dose is only for poorly soluble particles. Again, this table should be redone for rats using same inhaled particle size distribution as in humans.

Page 7A-13, table 13: In the title it should be made clear that the rat exposure was to the artificial resuspended particles followed by a 6-month ambient air exposure. Again, the use of resuspended particles in this model example should be reconsidered.

Line 12: An additional caveat that should be added here is: As with any model, there can be significant uncertainties around the predicted values; for example, the ICRP vs. the NCRP vs. the MPPD model for humans show significant differences for some particle sizes, although the general shape of the deposition curves is very similar.

Page 7A-14, line 13: Several scenarios are listed here for moving the rat into a "susceptible" condition in order to observe adverse PM effects: One is exposing the rat to a sufficiently high concentration of PM. However, a caveat should be added here that doing so may be very different from a compromised organ being exposed to lower concentrations, in terms of the underlying mechanisms causing an effect.

Also listed here is the possibility of reducing the rat's resistance by providing poor nutrition. A caveat here is that nutritional deficiency is not the same as a compromised organ; in fact, it has been shown in restricted diet studies that this may lead to greater resistance towards toxicity and carcinogenicity.

Page 7A-15, table 8: The rat instillation dose is given here as 20 μg, however, in the text it says 250 μg.

Line 5: Studies in rats and humans with CAPs are compared here, why is the MMAD for the rat CAPs so large, i.e., 1.96 μm? CAPs should have pretty much the original ambient size distribution.

Page 7A-17, line 1 and 2: This comparison of a bolus instillation dose with deposition from a single exposure day by inhalation is not adequate given that there is a huge difference in the dose rate, delivery within a second vs. delivery over 24 hrs., which makes a big difference in terms of acute effects.

Line 16: Why was in this example the rat dose compared with the human dose, given that the humans were already overdosed, and also were instilled as opposed to having inhaled the particles. The conclusion that the doses examined in rats were not overwhelming is based on the wrong premise.

Lines 24-28: The conclusion that the 25% difference between human and rat inhalation exposures was not substantial among the two instillation studies does not hold, given that the human dose is already higher than the actual dose that they would have received by inhalation; in addition there is the instillation bolus effect, i.e., the extremely high dose rate. Thus, one has to be very careful when interpreting results from dosemetric comparisons to avoid flawed conclusions. Was the predicted 24 hr. human exposure based on the high 40 L/min ventilation?

Page 7A-19, line 3: Zinc oxide particles inhaled are very well soluble in the lung, the retention halftime in rats is on the order of only 6 hrs.

Lines 10 and 11: Again, the statement that the findings with Utah Valley dust lent credence that instillation and inhalation studies provide complementary (misspelling) data and consistent conclusions, is not compelling: yes, within the two instillation studies they appeared to do that, but the EPM and Utah Valley emissions studies (inhalation vs. instillation) should not be used to suggest that inhaled and instilled doses give the same result, there are too many other examples showing that this is not the case (for summary of this topic the White Paper of the Inhalation Specialty Section of SOT has discussed this topic extensively and could be quoted here).

Page 7A-20 to the end: This summary needs to be modified, using results of an example where rats and humans are modeled as being exposed to the same real world particle size distribution; the reference in the rat should not be an artificial resuspended dust comparing this to human exposures with real world PM. Incidentally, with respect to resuspended PM, a new study by Gerde et al. has described a method by which a particle size distribution can be obtained with a mass median diameter of 0.5 μm of resuspended ambient dust materials.

Page 7A-21, line 1: The general statement that exposures in rats with higher concentrations of PM "would be justified to achieve nominally similar doses" compared to humans appears to be valid, but it should be made clear that these higher concentrations are not higher by a factor of 10 or 100-fold or even more, as is oftentimes the case.

Dr. Jonathan M. Samet

Comments: Revised Chapters 7 and 8, *Air Quality Criteria for Particulate Matter*

Jonathan M. Samet
Department of Epidemiology
Johns Hopkins Bloomberg School of Public Health
Baltimore, MD, USA

My comments will be limited to the revised Chapter 8 which addresses the epidemiological evidence. In many respects, there has been dramatic improvement in this chapter in comparison to the last version. In particular, there is a much more cogent and careful discussion of the complex methodologic issues that are relevant to interpretation of the epidemiological evidence, and throughout the document there has been greater care in applying a more uniform approach to evidence interpretation. Some inconsistencies remain, reflecting the multi-authored nature of the document. In general, I do not have overarching comments to offer. My specific comments are set out below:

- In discussing confounding and effect modification at the chapter's beginning, I suggest giving some consideration to the additional problem of exposure misclassification and its implications for interpretation of evidence, particularly if the degree of misclassification is differential among pollutants.

- To the extent possible, the graphical display approaches should be used in preference to lengthy tables. In general, the document's authors have used figures well, but there are additional opportunities to better display the data.

Page 8-37, Lines 28-29: This point needs expansion
Page 8-45, Line 7: or an indication of PM source
Page 8-46, Line 14: "are adequately modeling" By what criteria
Page 8-47, Lines 11-12: The issue is not which is "most appropriate", but sensitivity to model specification
Page 8-72, Line 12: This sentence seems overly strong in view of the limited evidence.
Page 8-78, Lines 18-21: The view should not be advanced that there is some "correct model"
Page 8-108, Line 21: Substantial seems overstated with only two studies.
Page 8-120, Lines 6-11: These studies are particularly valuable for causal inference, not quantification of risk.
Page 8-146, Line 1: These are studies of effect markers.
Page 8-154, Lines 18-23: This unreferenced material overstates the evidence on c-reactive protein and CVD and also on infections and CVD.
Page 8-156, Lines 15-18: This is rather simplistic; the elderly develop CVD.
Page 8-199, Lines 14-15: An overstated conclusion.
Page 8-201, Lines 1-201: I disagree; many analysts have explored model sensitivity.
Page 8-202, Lines 13-15: This is only one aspect of uncertainty.

Page 8-218, Lines 6-17: Certainly we know more about the gases than implied by this paragraph.
Page 8-221, Lines 1-12: Confusing paragraph.
Page 8-223, Lines 12-14: Meaning not clear
Page 8-250, Lines 2-5: I doubt that either PM or people vary widely across geographic locations as implied by this sentence.

Dr. Sverre Vedal

Critique of 2004 revisions of draft PM Criteria Document (chapters 7 & 8)
Sverre Vedal
February 3, 2004

Chapter 8:

1. General.

This revised draft includes some substantial improvements over the previous draft. There is even further improvement in the evenhandedness of the discussions (see #8 below). For example, the discussion of our understanding of relative effects of different PM size fractions (p.54 & p.59) is appropriately qualified. Absent are the "funnel" plots based on the NMMAPS data that did not make the intended points, and the somewhat peripheral, and difficult to understand, early discussion of effect modification. There is now some discussion in the text of revised GAMs individual-city studies. There is still a disheartening large number of errors that persist, even though these were pointed out at the last review period. See Specific &/or editorial comments, below.

2. Multi-city studies, including NMMAPS.

As noted above, some of the revised discussions involving NMMAPS are more true to the findings. The relationship between the precision of the individual-city effect estimates and the effect estimates themselves is clarified by noting that consistently positive effects in the cities with the most precise estimates is largely seen only in the Northeast US (p.258).

However, the argument that lower effect estimates tend to more commonly occur in cities having lower concentrations of PM10 persists (p.259, line 5). As argued during the last review period, this point was explicitly addressed by the NMMAPS investigators in their report, and the opposite is true: namely, there was a tendency for cities with the highest PM10 concentrations to have the smallest effect estimates.

Regarding the NMMAPS overall effect estimates, a somewhat mixed message is conveyed. It is initially stated (p.36, line 13) that NMMAPS provides "extremely useful information regarding...the magnitude of the combined PM10 effect estimate", but later (p.46, line 17) it is stated that this estimate "may well underestimate the PM10-total mortality effect size suggested by two other well conducted multi-city studies..." (effects based on much smaller numbers of cities) and that it reflects overaggressive control of temporal trends (p.47, line 1). Which is it?

3. Cohort studies.

This draft incorporates the new important findings based on the Hoek report from the Netherlands on the association between residence in proximity to large roadways and mortality. It should be noted that the effect estimate for black smoke (1.34) reported here in the summary of that report (p.115, line 27) is the unadjusted estimate. This estimate is decreased after appropriate adjustment for covariates, and approaches the null value when the analysis is limited to subjects who resided in the same area for a given number of years, indicating the likelihood of confounding using this exposure metric. These latter two (adjusted) estimates are those that

should be compared to those from other cohort studies (Six Cites and ACS, for example), and while not negating findings from those studies, does nevertheless add fuel to an argument that findings from the spectrum of cohort studies are not necessarily in agreement.

As I have mentioned before, a better job needs to be done to justify discounting the findings from the AHSMOG and Veterans study.

The discussion of the Lipfert and Morris study (p115, line 4) is confusing. It is noted that variables for some potentially relevant ecologic factors are included in their models and that this may explain their generally lower estimates of effect compared to the cohort studies. Is this appropriate adjustment for confounding, or is it felt that this is "overadjustment" and that the resultant estimates should be discounted?

In the summary of the cohort studies (pp.124-7) there was no mention of the Pope ACS extended analysis findings (JAMA 2002), particularly as regards lung cancer.

5. Particle composition.

In all discussions of the short-term effects of specific particle components there is invariably special mention of the effects of sulfate and acid aerosol. While it is correctly pointed out that in some studies in which no effects were identified, the concentrations of sulfate and acid aerosol were relatively low (e.g., Detroit), the body of data supporting effects of these components, particularly in light of toxicologic studies, is not very compelling.

6. Natural experiments.

This draft updates the findings from "natural" experiments by including the important findings from the recently reported studies from Dublin and Hong Kong (pp.118-9). There was some lack of evenhandedness in interpreting findings from Dublin in which it was argued that a PM effect was seen, as opposed to those from Hong Kong in which the "intervention" was largely limited to a decrease in SO2 concentrations. The latter is criticized, arguing that the interpretation of the "results is complicated by the upward trend in mortality due to the increase in population size and aging" (p.119, line 1). A similar yardstick is not applied to the Dublin study in which concerns over a decease in the prevalence of cardiovascular disease and, likely, a population that is not aging as is the rest of Ireland, could also contribute to declines in cardiovascular mortality in concert with the reduction in PM concentrations. To be fair, this tendency to interpret findings in a manner that is not evenhanded has largely been **expunged** from other parts of this draft of the chapter (see #8 below for examples of exceptions). Revision of this newly presented material on natural experiments will hopefully reflect this recent approach to interpretation that in fact characterizes most of this revised chapter.

7. Co-pollutants.

This draft deals more fairly with the role of the gaseous "co-pollutants". There is less space devoted to discrediting their role as potential confounding factors, and more space to presenting both single-pollutant model PM effects as well as multi-pollutant PM effects (e.g., Table 8-16). While the discussion on gaseous pollutant variable as possibly acting as surrogate measures of some features of PM composition (p.216) is illuminating, there is no mention that daily variations in the concentrations of these pollutants might also serve as measures of unmeasured features of meteorology, an equally credible possibility.

8. Evenhandedness of presentations and interpretations.

There has been a significant improvement in this draft in the evenhandedness of the interpretations. The sections on time series studies of hospitalizations and on effects on measures of cardiovascular "physiology" (p.153) are particularly improved in this regard.

There is still some lack of evenhandedness in interpreting some of the findings when they go against the preferred interpretation. For example, the time series studies of Canadian hospitalizations of Burnett, studies in which is was found that the effects of the gaseous pollutants overwhelmed those of PM, are criticized by noting that selection of day lags is "completely data driven" (p.140, line 16; p.141, line 13). This same criticism could have been leveled at almost every other time series study reviewed in this chapter, but was not.

A further lack of "parallelism", that in this instance needlessly runs the risk of confusing readers, concerns the depiction of effects of the GAMs default change and other revised analyses when comparing mortality and morbidity (largely hospitalization) studies. The change in the reanalyzed PM effect estimates on mortality, it is stated, "was in most cases less than 1% excess deaths per 50 mcg/m3 increase in PM10" (p.204, line 24) [strictly incorrect, in that in 7 of 14 instances the change is in fact 1% or greater (Table 8.34, p.205)]. There can still be confusion as to whether this means that there was less than a 1% change in the estimate of effect, a trivial change. This description is somewhat ingenuous in that a 1% change in excess deaths can be a large change relative to the original effect estimate, if that estimate was quite small, which many were. Adding to the confusion is the description of the change in the context of the hospitalization studies, in which the change is in fact described in terms of the percent change in effect estimate (p.210, lines 4-6), with in this case changes of from 20 to 29%. I would prefer to see the changes in mortality effect estimates presented as percent changes in the effect estimates, as they are for hospitalizations.

9. Susceptibility.

The discussion of susceptible population subgroups is also much improved and more fairly reflects the findings. For example, the description that findings on hospitalizations are not very consistent in demonstrating that the elderly are more susceptible (p.261) is more fair.

10. Statistical modeling.

I found this discussion (p.201 and on) helpful. There are a few exceptions. For example, use of a large number of degrees of freedom to control temporal effects in time series studies might indeed result in a less efficient estimate of PM (p.212, line 1), but this is not necessarily incorrect if control of confounding is the overriding concern.

Specific &/or editorial comments:

8-5, L23 & 8-6, L17: Prospective cohort studies should be distinguished from panel studies, since these are qualitatively much different.

8-12, L1-2: Temperature and humidity are rarely examined as effect modifiers in time series studies

8-12, L11: A change in effect estimate (without a change in standard error) is sufficient to suggest confounding. Leave out the reference to standard error in this context.

8-26: In the comments in the table on Gamble, how can NO_2 be both associated and not associated with mortality?

8-60, L2: In comparing this statement regarding the range of effects for PM2.5 (2%-6%), I find that the findings depicted in Table 8-5 (p.57) do not leave me with that impression.
8-66, L2 & 8-76, L3: The Goldberg study did not investigate deaths due to CHF, but instead looked at total mortality in the stratum of subjects with pre-existing CHF. This needs correcting.
8-107: The last AHSMOG superscript referring to the reference should also be "9".
8-138, L13: Why is there a reference to work in press?
8-146, Figure 8-10 & 8-178, Figure 8-12: What is the basis for selecting the specific studies included in these plots?
8-156, L21: I continue to correctly dispute this sentence that claims adequacy of control for weather.
8-201, L14-15: I don't agree that there is an assumption that the best fitting models are associated with the largest and most significant PM effect estimates. Clarification is needed.
8-202, L13, etc: The depiction of the p-value or confidence interval as indicating anything about whether a finding is "real" or due to statistical artifact is incorrect.
8-209, Figure 8-16: The fact that the correlations in this plot are high is almost meaningless. More emphasis should be placed on the actual differences due to the revised analyses. I would drop the figure.
8-250, L2-5: The fact that various mortality outcomes might have different lag structures has nothing to do with the lag structure for a given outcome across cities. Clarify this sentence.
8-259, L29: "HEL" should be "HEI".

Mr. Ronald H. White

Comments of Ronald White, M.S.T.
Chapter 8 of Air Quality Criteria for Particulate Matter
(Fourth External Review Draft)

General Comments

This version of Chapter 8, "Epidemiology of Human Health Effects Associated With Ambient Particulate Matter", substantially improves on the previous edition in the Third External Review Draft of the Particulate Matter Criteria Document. Overall, there is a more balanced tone to the discussion of the linkage between particulate matter of different size ranges and composition to health outcomes, including an improved discussion of the uncertainties associated with interpreting these studies such as the potential role of other air pollutants in contributing to the health outcomes being assessed in these studies. The criteria delineated on pages 8-4 to 8-5 that provide the basis for selection and assessment of the studies included in the chapter are reasonable and provide some needed transparency to this process.

The revised discussion of the issue of confounding by co-pollutants and other cofactors reflects an improvement in the discussion of this issue, though some additional "fine tuning" of this language could improve the clarity of the discussion. The addition of the more recent "intervention" studies improves the strength of the discussion of these types of analyses.

Though Chapter 8 can still benefit from some additional copy editing to provide a consistent voice to the text, the chapter in its current form represents a comprehensive review of the particulate matter epidemiologic health effects literature from 1996 to 2003, and is in sufficient condition to warrant closure with some additional revisions to address the detailed comments from the CASAC panel on this chapter.

Detailed Comments

Pg. 8-35, line 8: The reference to the revised NMMAPS effects estimate of 0.21% per 10 ug/m^3 is specific to the GLM with natural splines model. The coefficient for the revised GAM model of 0.27% per 10ug/m^3 should be mentioned here as well.

Pg. 8-37, lines 28-29: This is a significant issue that deserves an expanded discussion in this section.

Pg. 8-57, Figure 8-5: The publication date (2000) for the Cifuentes et al. study has been omitted.

Pg. 8-59, lines 12-14: As noted by Dr. Koenig in her comments, some discussion of the significantly larger relative risk estimate for cardiovascular mortality found in the Mar et al. studies (2000, 2003) in comparison to the other studies included in this section would be appropriate.

Pg. 8-66, lines 21-22: The fact that the mean H^+ value reported in the Brook et al. (1997) study is noted as almost 50% below the measurement system's detection limit calls into question the accuracy of the results from this component of the study.

Pg. 8-90, line 2: Typo, strike "d" in "dof".

Pg. 8-96, line 23: If the intent of the word "significantly" is to imply statistical significance, it should be stated as such.

Pg. 8-118, lines 3-4: This seems to overstate the findings on the "harvesting" issue. Rather than a "lack of evidence", it would be more appropriate to indicate that the preponderance of evidence indicates that short-term "harvesting" does not fully explain the periodicity and magnitude of mortality associated with PM exposure.

Pg. 8-120, lines 14-15: While the authors do report a decrease in ambient PM_{10} level, the appropriateness of retaining discussion of the Friedman et al. (2001) study on the impact of traffic volume reductions during the 1996 Olympics in Atlanta is questionable given the emphasis in the author's discussion of the study findings on changes in ozone levels and asthma morbidity.

Pg. 8-171, lines 7, 8,11: The reference to coarse particles as "$PM_{2\ 5\text{-}10}$" is inconsistent with the reference to coarse particles as "$PM_{10\text{-}2\ 5}$" in line 13 and in the remainder of the CD chapter.

Pg. 8-174, line 5: Text seems to be missing here.

Pg. 8-246, lines 22-23: See above comment regarding inclusion of the Friedman et al. (2001) study.

Pg. 8-287, line16: The PM metric used in the Brunekreef (1997) study to estimate life-shortening should be referenced.

Dr. Warren H. White

Comments on December 2003 draft CD Chapter 8, by Warren H. White

This draft is well written and gives a useful review. I have two caveats to suggest, though.

8.2.2.3.4 Comparison of effects estimates from multi-city studies

The discussion on pages 8-45,6 discounting the lower values from NMMAPS as likely being due to over-"aggressive" treatment of weather effects is a bit tendentious. It makes the point that NMMAPS used "four separate weather terms" whereas "most of the other studies used only one or two terms for weather variables." But climatologists who study weather and pollution effects on mortality from their own perspective

> "suggest that in trying to separate weather from pollution, other research methods may de-emphasize the impact of weather while possibly exaggerating the impact of pollutants. For example, rarely has previous research recognized the importance of synoptic *situations* ... Rather, previous studies have relied on individual meteorological variables ... to assess the impact of weather on human mortality." (Smoyer et al., 2000)

Now, it's true that the biometeorologists don't do as good a job with the PM as "our crowd" does; the quoted paper employs TSP and ozone rather than PM_{10} or $PM_{2.5}$, for example. On the other hand, they do start with some credibility in their assessment of our met modeling. The draft prefers the approach taken to the Harvard Six Cities time series, but I doubt that those authors (Schwartz et al.) successfully captured the 57% increase over previous years in all-cause July deaths from the 1980 heat wave in St. Louis, one of the two cities driving their overall results. (The toll was 64% in Kansas City, arguably indicative of Topeka.) "About one of every 1000 residents of both cities was hospitalized for or died of heat-related illness." (Jones et al., 1982). That's an "aggressive" weather effect!

The draft also questions the inclusion of dewpoint in the models when "in fact, dewpoint and temperature are highly correlated", arguing this means "the epidemiologic implications of the use of these terms is not yet clear." But again, there's a reason why the familiar "heat index", or "apparent temperature", "temperature-humidity index", or "discomfort index" is sensitive to dewpoint and is not just a multiple of temperature, and there's a reason why people want forecasts of it. Of course T and DP *correlate* well: but going from (T,DP) = (70°,69°) to (T,DP) = (100°,99°) is a whole lot more stressful – in obvious physiological terms – than is going from (T,DP) = (70°,60°) to (T,DP) = (100°,90°)!

The draft finally concludes that NMMAPS modeling "most likely provides 'conservative' PM risk estimates" that "may well underestimate the PM_{10}-total mortality effect-size". I have no problem believing that NMMAPS provides *more-conservative* estimates than the other studies, but why should I believe that NMMAPS is wrong and the others right?

8.4.10.2 Life-shortening estimates based on semi-individual cohort study results

Bert Brunekreef's (1997) life-table estimate is later (page 8-289) featured as number 6 in a listing of "The most salient conclusions derived from the PM epidemiology studies". If it is to bear this much weight, it deserves a little closer examination than is done in this single paragraph. How sensitive is it to his assumption – which the cohort studies did not test – that the relative risk from PM is constant after age 40, rather than increasing with cumulative exposure as might seem more likely?

References:

T.S. Jones, A.P. Liang, E.M. Kilbourne, M.R. Griffin, P.A. Patriarca, S.G. Wassilak, R.J. Mullan, R.F. Herrick, H.D. Donnell Jr, K. Choi, and S.B. Thacker (1982) Morbidity and mortality associated with the July 1980 heat wave in St. Louis and Kansas City, MO. JAMA 247, 3327-3331.

K.E. Smoyer, L.S. Kalkstein, J.S. Greene, and H.Ye (2000) The impacts of weather and pollution on human mortality in Birmingham, Alabama and Philadelphia, Pennsylvania. International Journal of Climatology 20, 881-897.

Dr. George T. Wolff

Comments on Chapters 7 and 8 of the December 2003 Criteria Document for Particulate Matter

George T. Wolff
(1/30/04)

Chapter 7

The deposition calculations that appear in Appendix 7A are not what I expected. I thought CASAC asked to see is a simple estimate of the total deposited doses of PM to the alveolar region of the human lung for say a 10 $\mu g/m^3$ increment of $PM_{2.5}$ over a 24 hour period. This would be expressed as a total and per unit surface area of lung. I still would like this calculation included.

Chapter 8

General Comments

The focus of this chapter is to make the strongest case possible for a causal PM2.5/mortality relationship. In focusing on this, many of the subtleties that need to be discussed of the now huge epidemiology data base are ignored. First, while there is a growing body of studies that show a significant positive relationship between PM and mortality, there are also growing bodies of studies that show no effect or implicate one or more of the other criteria pollutants or PM10-2.5. In addition, these bodies would likely be bigger if there was no publication bias.

The heterogeneity of the results gets some attention in the chapter but only with respect to NMMAPS. When you look at the bigger picture of all the studies (mult-city, single city, morbidity studies etc.), you see a wide range of heterogeneity across all the studies. Coefficients for effects vary, health outcomes vary, pollutants implicated vary, and model specification vary. There is no consistency.

It is particularly interesting to look at the results in cities where multiple studies have been conducted. I refer to the November 2003 comments submitted by AIR, Inc on the Staff Paper. These studies show little agreement with respect to the pollutants implicated or the specific health outcome. How can this be explained?

The recent revised analysis precipitated by the GAM fiasco produced some amazing revelations concerning our ignorance about the time series studies. In their commentary, the HEI review panel state: "Neither the appropriate degree of control for time in these time series analyses, nor the appropriate specification of the effects of weather, has been determined." To me this says we cannot trust the results of these time series studies. This notion is further supported by the results of Lumley and Sheppard (Epidemiology 14:13-14, 2003), Smith et al. (NRCSE-TRS 66,

2001) and Koop and Tole (J. Envir. Economics and Mgt. 47: 30-54, 2004). In the Koop and Tole article, the authors argue that the results of a single time series model should not be trusted. They recommend that a suite of models be applied and model uncertainties be calculated. However, when they do this, the standard deviations for the air pollution/mortality impacts become so large, they question the plausibility of the previously measured links between air pollution and mortality. Since this Koop and Tole article is potentially a show stopper, it should be dicussed in the CD.

The chronic studies have some problems as well that need further addressing. The first is respiratory effects. Most of the time-series studies show a respiratory effect. Why don't the chronic studies? It does not make sense.

There is also the issue of the "weight of evidence." What is the "weight of evidence"? There are in essence 4 chronic studies discussed in the CD. Two show significant PM/mortality signals: ACS and HSCS. Two show none: VA and ASHMOG. EPA inappropriately dismisses all the VA results and most of the ASHMOG results. But there is more information here. In ACS and HSCS, the PM effect was statistically significant only for those with less than a high school education, and in ACS only for those who lived in the eastern U.S. (the HSCS did not have any western cities). So what is the "weight of evidence" now? The studies that show no effect are: VA, ASHMOG, ACS (for people with a high school education of higher and those people who live in the Western U.S.), and HSCS (for those with better than a high school education).

There is also the issue of SO2. The HEI ACS reanalysis included some sensitivity analyses and indicated that SO2, not PM2.5, was the stronger and more robust indicator of mortality. This finding is dismissed as biologically implausible because of the low SO2 concentrations. However, after 7 years of extensive, intensive, focused toxicological research, a plausible biological mechanisms to explain how PM is causing mortality at today's ambient US concentration have not been found. How can SO2 be dismissed, but not PM?

Specific Comments

p.8-18, line 7- Missing from here is a mention of the other important results from Klemm and Mason – their sensitivity analyses.

p. 8-19, lines 19-29 – "interpreted with caution"? We should dismiss the results because of the GAM problem. We have no confidence in any of these results.

p. 8-21, line 16 – Again there is no mention of Klemm and Mason's other important results.

p. 8-21, lines 27-32 – It should be pointed out that the HEI commentary from the revised analyses raises questions about these issues again, especially the first two issues.

p. 8-30, line 20 – It should be pointed out that in the reanalyzed NMMAPS, lags 0 and 2 are no longer statistically significant.

p. 8-34, line 8 – Figure 8-4 is misleading. Each curve in the figure is based on a different group and different number of cities. They must be based on the same group of cities before any conclusions can be drawn.

8-34, line 16 – For lag 1, the associations of the gases with mortality are similar to the PM/mortality association.

8-39, line 14 – It should be mentioned that the 1% result was not statistically significant.

p. 8-46, lines 15-17 – This is pure speculation.

p. 8-47, lines 11-15 – So how do you pick the right model?

Section 8.2.3.2.4 The VA Study – Even though the 2003 reference is now included the treatment of this study is not the same as the ACS or HSCS. It should be given equal value.

p. 8-105 – There should be a table here showing all the results from the VA study like was done for the other cohort studies.

p. 8-107, Table 8-11 – There is much more information from the VA study that belongs in this table. The VA also has 15-2.5 data, PM15 data and data for two different time periods.

p. 8-108, lines 14-15 – The opposite can be said too. The tone of this sentence is inappropriate.

p. 8-108, lines 15-16 – The ACS study may have had a larger population, buy 58.9% of the subjects who had more than a high school education did not respond significantly to PM.

P 8-108, lines 18-21 – See my general comments on this subject.

Tables 8-14 and 8-15 – The VA study results should be included here. The reasons given in the text are inappropriate.

p. 8-115, line, 10-11 – For a number of reasons the Hoek et al should not be emphasized. It is riddled with questionable assumptions and methodology. I refer the Agency to the comments submitted by Ford Motor Company on this chapter. They include an excellent critique of this study.

Section 8.2.3.4 – I question whether any of these studies can attribute health benefits unambiguously to PM. Others have attributed the Utah study to lower respiratory virus infections that winter. In Dublin, SO_2 and PM decreased and NO_2 and CO probably did as well. In Hong Kong, PM stayed the same but SO_2 decreased.

p. 8-112, lines 26-31 – I commented before on this and no changes were made. This mischaracterizes Lipfert et al (2000C) which totally negate the results of Woodruff et al. I suggest the Agency read the comments on this chapter prepared by Fred Lipfert and make appropriate changes.

p. 8-123, line 10 –Chay and Greenstone (2001a,b) – There is only one Chay and Greenstone listed in the references and it is not peered-reviewed.

p. 8-201, entire page – This is a great discussion. Based on this, how can we accept the time-series studies as being causal?

P 8-214, lines 1-10 – Another great discussion which makes an objective person question the results of NMMAPS and all other time series studies.

P 8-215, line 3 – This statement is meaningless if all the other statements on the page are true.

P. 8-259, line 6 – This is not true.

NOTICE

This report has been written as part of the activities of EPA's Clean Air Scientific Advisory Committee (CASAC), a Federal advisory committee administratively located under the EPA Science Advisory Board Staff that is chartered to provide extramural scientific information and advice to the Administrator and other officials of the Environmental Protection Agency. The CASAC is structured to provide balanced, expert assessment of scientific matters related to issue and problems facing the Agency. This report has not been reviewed for approval by the Agency and, hence, the contents of this report do not necessarily represent the views and policies of the EPA, nor of other agencies in the Executive Branch of the Federal government, nor does mention of trade names or commercial products constitute a recommendation for use. CASAC reports are posted on the SAB Web site at: http://www.epa.gov/sab.