



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

OFFICE OF THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

August 16, 2004

EPA-SAB-CASAC-04-008

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 in a public meeting held in Research Triangle Park (RTP), NC, on July 20-21, 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). The current Panel roster is found in Appendix A of this report.

This meeting was, in part, 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. As noted below, the Panel held extended discussions with EPA staff members on the plans for the completion of the AQCD for PM. The revised draft 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 were provided to the Panel and the public in mid-June, and a completely-revised Chapter 9 (Integrative Synthesis) was similarly provided on June 28, 2004.

The focus of this July 20-21 meeting was for the CASAC PM Review Panel to review these revised Chapters 7, 8, and 9 and the associated appendices of the AQCD for PM. After extended discussion, the Panel concluded that these chapters had been sufficiently improved that it could close on Chapters 7 and 8, with the understanding that the Agency's National Center for Environmental Assessment (NCEA)-RTP will make further revisions as necessary to address the

issues raised both in this report and in the Panelists' individual review comments provided in Appendix B of this report.

However, although the Panel considered the rewritten Chapter 9 to represent a very good initial effort toward developing an integrated synthesis of the information in the AQCD for PM, the chapter was judged to require sufficient additional revisions that the Panel felt a subsequent review would be necessary before it could come to closure on this chapter. In addition, if there is to be an Executive Summary (which was not provided in these latest revisions) to the document, this would also need to be reviewed by the Panel prior to closing on the entire AQCD for PM. Nevertheless, with appropriate attention, the Panel thinks that the current version can be brought to a point where it will be adequate for closure in a relatively short time.

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, which is administratively located under EPA's Science Advisory Board (SAB) Staff Office, is a Federal advisory committee chartered under the Federal Advisory Committee Act (FACA), as amended, 5 U.S.C., App.

EPA is in the process of updating, and revising where appropriate, the AQCD for PM as issued in 1996. A detailed history of this current, ongoing review is contained in the Background section of the CASAC PM Review Panel's 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 Panel's most recent report on this topic (EPA-SAB-CASAC-04-005, dated March 1, 2004) was prepared following the public teleconference held on February 3, 2004. Both of these documents can be found on the EPA Web Site at: <http://www.epa.gov/sab>.

2. CASAC PM Review Panel's Ongoing Review of the Revised Chapters 7-9 of the EPA Air Quality Criteria for Particulate Matter (Fourth External Review Draft)

Chapter 7 (Toxicology)

Chapter 7 was deemed to be substantially improved from the prior version. Numerous previous content issues have been resolved, and the text is much cleaner. The major problem that remains is the Chapter's Integrative Summary section. It is missing various key points such as the fact that Concentrated Ambient Particles (CAPs) used in most of the cited studies do not concentrate the gaseous phase and ultrafine particles (< 0.1 μm). Also, the summary needs to include a mention that the dosimetry modeling predictions describing the doses in the animal and some of the human studies were relatively high and the relevance of the results to real world exposures is uncertain.

The draft PM AQCD covers relevant papers published prior to April 2002. The Panel discussed the inclusion of papers published after April 2002. For consistency, the Panel

recommends that the Reed *et al.* (2004) paper not be included. Although the paper adds to the overall body of information, it does not make any substantive change in the overall evaluation of the effects of airborne particulate matter from controlled exposures to animals or people.

The material presented in Chapter 9 on the potential role of particle-bound water on the toxicity of the particulate components should be in Chapter 7 rather than Chapter 9. In addition, the study by Morio *et al.* (2001) presented in Chapter 9 also needs to be introduced in this chapter. Chapter 9 can then appropriately reference the Chapter 7 material. The section summarizing the information currently available should take care to note the limited amount of information currently available and the need for follow-up studies.

Appendix 7A

Appendix 7A on rat to human dose extrapolation provides valuable information for putting into perspective the relationship between various exposure levels and instillation doses used in animal studies relative to the comparable kinds of exposure levels or doses that would be needed in humans. All of the calculated values are presented with a high degree of apparent precision (two or three significant figures). However, it should be recognized that they are the results of model calculations and in the absence of further validation should be used and interpreted with caution. Thus, it is likely that no more than two significant digits should be used and appropriate caveats provided regarding the likely accuracy of the results.

Unfortunately, some of the appendix examples have failed to find their way into Chapter 7. Specifically, there is no material in the new Section 7 of Chapter 7 that relates to the intratracheal instillation studies for the Utah Valley dust used in human and animal experiments. The important issue of dose vs. dose rate should be addressed in this context. This is a major omission that needs to be corrected. To their credit, the authors have included in Section 7 examples of inhalation studies with CAPs as well as *in vitro* experiments and the relevant kinds of interspecies dosimetric comparisons that enable judgments to be made about the potential extrapolation of the effects seen in the animal studies.

The instillation studies need to be also covered in Chapter 7 because of the discussion in Appendix 7A in which the authors of the human and animal studies using the Utah Valley dust incorrectly reported what would be equivalent exposures or typical community exposures associated with their instillation doses. For example, instead of a single day or up to one week of exposure for the human instilled doses as stated by Ghio and Devlin, exposures would need to be on the order of two months. Since EPA has placed great weight on the apparent similarity of results between studies with the Utah Valley dust in animals and humans, it is imperative that Chapter 7 correctly portray the relevance of these instilled doses to real world ambient exposures. Similarly, while Table 7-15 is a useful addition to the new Section 7.7, the discussion in the text surrounding this Table is still not sufficient to put the *in vitro* doses into proper perspective. Doses are reported in terms of nanograms per cell estimated from information in the publications, and most readers would interpret these doses as being low rather than high. However, taking into account the density of the cells on the plates and the mass associated with a single particle, the lowest doses reported still involve each cell receiving anywhere from about 25 to 400 particles, which is not a small dose. That being said, Table 7-15 helps to establish a dose response relationship for the effects of PM on alveolar macrophage phagocytosis.

Appendix 7A contains information on comparative biological responses that belongs in the main body of the chapter. It is exactly for the purpose of appropriately comparing the findings of animal studies to human study results that the comparative dose modeling is required. The purpose of the appendix is to provide a foundation for judging the value of animal study data, with the comparison of animal and human responses included in the body of the Chapter 7. The health response comparisons belong there, not here.

The Appendix would be substantially improved by clearly identifying the very few biological observations that provide the basis for the extensive mathematical extrapolations. The text should reflect that some of the calculated parameters such as deposited or retained dose per unit surface area are unlikely to ever be actually measured. Thus, all of the table and figure captions should be reviewed and the words “estimated” or “calculated” be placed in front of any estimated or calculated quantities.

The Appendix would be substantially strengthened by including “measured” values for comparison with “calculated” values. For example, “measured” lung burden data from the study of Wolff *et al.* (1987), [Alterations in Particle Accumulation and Clearance in Lungs of Rats Chronically Exposed to Diesel Exhaust, *Fund. Appl. Toxicol.* 9: 154-166] of rats exposed to diesel exhaust could be plotted in Figure 7A-8.

Overall, Appendix 7A provides good and thoughtful discussions. However, it would be desirable to include some concluding comments after the individual sections as done in the summary. Specifically, it would be useful to more fully emphasize the complexity of dosimetric extrapolations, stressing that this is highly dependent on PM parameters, exposure scenarios, breathing and activity patterns of different species and — not yet achievable by models — expected differences between responses of a compromised host vs. healthy host. The summary does a nice job in this regard, and conclusions in between individual sections would strengthen this.

Page 3, line 22 and subsequently throughout the appendix and figure legends, the Panel suggest not to use the term “highly insoluble” particles, but rather to call them “poorly soluble” particles. Although this term “highly insoluble particles” has been used in a number of earlier publications, the consensus in the toxicological community is that these particles should more appropriately be called “poorly soluble particles” because there is no particle which is highly insoluble (perhaps iridium is the most insoluble particle so far tested). The key is to make it clear that particles whose solubility is not a significant factor in relation to the time scales of clearance or retention; i.e., the time scales of observation.

Appendix 7B

A new appendix on ambient bioaerosols has been added to Chapter 7 as Appendix 7B in response to prior suggestions to move this material from the body of the Chapter. This appendix inundates the reader with information about fungi, bacteria, viruses, pollens, plant fragments, etc. Unfortunately, most of the information indicates the quantities that are present in the air in various locations and seldom presents effects of this material on humans or animals. If the Agency is presenting the information on ambient bioaerosols as part of a case for the interaction or synergism of these materials with other components of the ambient PM, the authors have an

obligation to report effects seen in animals or humans with these materials and at what levels these effects are seen. Failure to do so provides an open end for an argument of their importance when such is probably not the case. For example, Section 7B.2.1 describes atmospheric levels of cellulose and reports them to be typically less than $1 \mu\text{g}/\text{m}^3$ in the air and in some locations up to around $6 \text{ F g}/\text{m}^3$, yet there is no discussion of studies that have been conducted on the effects of cellulose in animals or humans. In his comments on this chapter, Panelist (and CASAC member) Dr. Fred Miller has provided about 25 references to studies where cellulose exposures to animals or humans were in the mg/m^3 or greater range with very little if any effects of the material on human health outcomes. Thus, if there is going to be emphasis on the presence of biological materials like cellulose, then there needs to be the commensurate discussion of what is known with respect to health effects. This disparity in coverage between exposure and effects is of concern and needs to be rectified. On a broader basis, the treatment of bioaerosols in the interpretative summary of PM toxicological findings in Section 7.9 falls short of delivering a punch line in relationship to the constituents of PM that EPA would propose to regulate in any standards that are revised or added.

There are a number of specific suggestions for revisions to the Chapter and its Appendices that have been provided in the Panel members' comments that should be considered as they will further improve the presentation.

Chapter 8 (Epidemiology)

With respect to Chapter 8, the Panel concluded that the revised version has now achieved a much better balance and is a fair representation of the wealth of epidemiological studies. The primer on epidemiology has been substantially improved although it still may provide statements that are too sweeping and these have been noted in the individual comments. The chapter properly offers the view that "correct" models can never be identified and that there is always a potential for residual confounding. This proposition is hardly unique to studies of particulate matter and health and has not been a barrier to the use of observational evidence in other contexts. Confounding is of greater concern when effect sizes are small, as in this case. However, the sweeping generalizations need to be toned down. The chapter begins with a description of the "Hill" criteria for causality, but these criteria are in fact not uniformly applied, either in this chapter or in Chapter 9.

There is again reference to both respiratory hospitalizations and mortality (p.9-126, L8) in the description of the Utah Valley steel mill closure. The formal study that directly used the steel mill closure in the design only involved respiratory hospitalizations. Mortality was only analyzed using a traditional time series design (Pope 1992). In that paper it was stated that average deaths per day were 3.2% higher when the steel mill was open than when it was closed. The baseline daily mortality was 2.7 deaths/day, which translates to less than a 0.1 death per day increase with the steel mill open. The absence of statistical power here explains why this "finding" has received little attention, quite correctly, except in this PM AQCD. The continued reference to mortality here in the AQCD is not justifiable, at least without appropriate qualifiers.

The discussion on gaseous pollutant variables as possibly acting as surrogate measures of some features of PM composition continues to be illuminating. However, there is too much made of this point (pp. 9.229-231, and elsewhere) since it remains highly speculative. As has

been noted previously, a more cogent argument can be made that daily variations in the concentrations of these pollutants serve as measures of unmeasured features of meteorology, given that meteorology is the primary determinant of daily concentration changes and, arguably, a more plausible cause of these health effects than the small daily concentration changes in either PM or the gaseous pollutants. There needs to be care to provide such alternative interpretations.

Section 8.4 is very well written and as will be discussed below, it might be better to use much of this material in Chapter 9 in place of the comparable section that is currently in that Chapter.

There was a discussion whether to consider the inclusion of the Hoek *et al.* paper (2002). Clearly it was critical to include work on the GAM reanalyses and the Panel had also requested the inclusion of the Hoek *et al.* paper. However, there are concerns about the use of several of the exposure metrics such as NO₂ and black carbon in this paper. The results using these exposure metrics need to be more carefully caveated or excluded from the discussion. Another problem is with the studies of motor vehicles from periods when leaded fuel was still in use. The emissions from those vehicles are very different than the emissions from current generation, catalytic-converter vehicles and appropriate discussion of this issue is needed. The Panel believes that the updated results from ARIES presented by Metzger *et al.* (2004) should not be included in this version of the PM AQCD, and that appropriate discussion of the problems of preliminary publication of partial results such as in the Tolbert *et al.* (2000) paper should be included in the chapter.

Two panel members and a number of public commenters argued for the inclusion of the Koop and Tole (2004) paper which addresses the “correct” model issue and questions the legitimacy of the model selection procedures used in most of the time-series studies that have been published. After a lengthy discussion by the panel and the Agency, it was decided not to include this paper, but to expand the discussion of the Clyde *et al.* (2000) paper which raises some of the same issues.

In conclusion, this revised draft of the PM Criteria Document chapter on the epidemiological evidence of the health effects of particulate matter improves on an already encyclopedic and generally well written review of the scientific literature published since 1996 on this topic. The authors have adequately addressed the vast majority of CASAC’s prior criticisms and suggestions for improvements of the previous draft document. The remaining comments in the Appendix should be relatively easy to address in developing the final version.

Chapter 9 (Integrative Synthesis)

Chapter 9 has been completely rewritten based on the discussions of the Panel’s meeting in August 2003, the outline provided to the Panel in September 2003 by NCEA, and agreed to by the Panel in its teleconference in October 2003. This initial version was a very good draft, but clearly suffered from time constraints that prevented full consistency in presentation and style. The Panel felt that the Chapter was too long and that the length was due to too much discussion of specific studies rather than synthesizing the detailed material presented in the earlier chapters. The key is that the information presented in the earlier chapters should be synthesized into a description of the Panel’s current level of understanding with respect to the organizing questions.

The Panel recommends that most references to specific papers be eliminated except in those limited cases where specific seminal facts are presented that require a reference. This approach will require more synthesis and less excessive detail that tend to lose the big picture thread that should be provided in this chapter. This was felt to be particularly the case for the toxicological question (Section 9.2.3) which currently represents about one third of the text in this chapter. As a result, it is the Panels' recommendation that an effort be made to limit this chapter to no more than 75 pages.

For example, the discussion of the potential role of particle-bound water belongs in Chapter 7 along with the Morio *et al.* reference. Then an appropriate summary can be provided in Chapter 9 as part of a real synthesis of the information in Chapter 7.

There was also strong concern for a lack of "bottom line" conclusions in the Summary and Conclusion sections. What is the level of understanding with respect to the questions that are posed as the integrating basis of the Chapter? The threads of the discussion need to be pulled together better so that the reader knows what the takeaway messages are. Clear conclusions will be particularly important if there is to be no Executive Summary as was discussed as an option.

The chapter suffers from an overuse and excessive reliance on the term "coherence" which is used in multiple ways. Although consistency in results among studies, etc. is helpful in evaluating the totality of the evidence, the discussion needs to be more even across the questions and use established evaluation approaches. The Panel cautions that the EPA should not be developing approaches to the evaluation of evidence (*i.e.*, are based on "coherence") that may differ widely from the approaches taken in other Agency reviews. Models for evidence evaluation are available from reports of the Surgeon General ("The Health Consequences of Smoking," May 2004) and the National Research Council (NRC), for example.

Throughout Chapter 9, there is an excessive use of adjectives such as "considerable," "strong," "very," "extensive," etc. such that the reader gets the impression that a "harder sell" is being made than what may be warranted by the data contained in the first 8 chapters of the PM Air Quality Criteria Document. Although the portions of the Chapter on epidemiology and toxicology were deemed too long because of the insufficient level of aggregation of information from the prior chapters, there was concern that many of the caveats and uncertainties described appropriately in the earlier chapter are not adequately reflected in Chapter 9. Thus, more balance is required in the synthesis and presentation of the integrated information.

In some cases the descriptive adjectives and hard-sell approach are also evident in sections that consistently emphasize the absence of effects associated with "crustal" components of PM_{2.5}, PM₁₀ or PM_{10-2.5}. For example on p. 9-44, line 18, it states that "Also of much importance, all of the above studies that investigated multiple source categories found a soil or crustal source that was negatively associated with mortality." The irrational implication that we would live longer if it were dustier needs some additional discussion, and it may be "of much importance" as it reveals poorly formulated models. In other cases, coarse metals, coarse wood smoke and/or pollen are proposed as likely causal factors for adverse health effects in arid

southwestern locations where coarse crustal particles and associated soil-borne fungi or bacteria might provide an equally plausible or more plausible explanation.

As indicated above, Section 8.4 was found by several of the epidemiological experts on the Panel to be a good model for much of the epidemiological discussion that is in Chapter 9.

One specific issue that was given too brief mention in the chapter, and needs some additional discussion is the timing of PM exposure with acute cardiac-related health effects and asthma. These findings appear to be potentially important and the results have implications for the averaging time and the form of the standard with respect to an acute PM_{2.5} health standard. It was the view of the Panel that the science is not yet adequate to support promulgation of a sub-24 hour health standard at this time, but these initial results indicate that more attention must be given to this issue in the future when more time resolved measurement data will be available. It would be helpful for this chapter to provide a short discussion on these findings.

In general, it was felt that the welfare effects of PM and the associated desirability of a possible secondary standard for PM were dealt with in too cursory a fashion. These welfare effects include: (1) visibility impairments in urban, rural, and park settings; (2) ecosystem responses to increased atmospheric deposition of the nutrient substances in PM; (3) direct effects of PM on materials — such as soiling of painted surfaces, exposed textile materials, etc.; and (4) potential impacts from PM contribution to climate change. This section also needs clear “bottom-line” conclusions as to what scientific conclusions about welfare effects should be drawn from the information presented in this AQCD for PM.

With respect to visibility and some of these other welfare effects that involve monetary valuation (see page 9-102 line 25, page 9-105 lines 15-23, and page 9-106 line 3), a broader approach may be preferred to blend the relevant information and messages from the newer studies (*e.g.*, the cited Denver/Phoenix studies that are about perceptions and attitudes about what constitutes adverse conditions) and the older economic studies (where monetary valuation is emphasized in as an indicator of adversity).

The PM AQCD does little in Chapter 4 to meaningfully combine information from the old studies and the newer studies identified to address relevant questions such as “how much or what characteristics of impairment are adverse?” and “how adverse is it?” This limitation carries on in Chapter 9 on page 105.

On page 9-106, lines 1-4, it could be noted that these local visibility standards have (at least in the case of Denver) resulted in PM_{2.5} emissions and concentration reductions. Given that there is a very good correlation between visual range and PM_{2.5} concentrations, it would be helpful to indicate the approximate PM_{2.5} mass concentrations that correspond to the various visual range values that are discussed. It would be useful to include that “similar threshold determinations, convergent on a minimal visual range of 40 to 50 km have also been identified in visibility standards in Lake Tahoe, the Fraser Valley of British Columbia, and state of Vermont. Thus there are more than two locations picking similar “adverse thresholds” and thus suggesting that this range might be one at which the public feels comfortable about the air quality. Such a

conclusion would clearly assist EPA's Office of Air Quality Planning and Standards (OAQPS) in assessing the need for secondary standards to protect visibility.

Further, regarding visibility impairment, EPA should note that a sub-daily secondary standard for non-Class I areas may be desirable and feasible, reflecting that: (1) visibility impairment is an instantaneous effect of PM_{2.5}; (2) daylight visibility is more important to most people, and is not adequately addressed by a 24-hour standard; and (3) recent local government initiatives and public value studies indicate that current PM secondary standards are not providing the desired levels of protection.

The authors are to be commended for concisely bringing together the key scientific information/understanding on vegetation and ecosystems from Chapter 4 as well as identifying the important data gaps and uncertainties which currently prevent relating ambient concentrations of PM to ecosystem response. The discussion of the potential application of the "critical loads concept" in the U.S. opens a very important philosophical/scientific door for environmental protection in the future. However, since Europe has long ago adopted the critical loads approach, it is time for the United States to consider very carefully why this approach is so widely used and widely accepted in Europe but has not really been considered very carefully here in the U.S. in recent years. It would be useful to bring forward this information so that there can be more vigorous efforts to move in this same direction in the near term future. It would also be useful to include in the environmental effects summary, the growing body of literature on the effects of crustal particles (and associated soil-borne fungi and bacteria) deposition on marine ecosystems — for example, the association between *Aspergillus* fungi and coral reef decline.

The section on materials damage is quite weak. Effects from PM and precursors are significant, but are considered less here than in the 1996 PM AQCD or the National Acid Precipitation Assessment Program's (NAPAP) State of the Science and Technology documents. Although there has not been a lot of new work done since these documents, it does not mean that materials effects should be described in such meager terms. It might also be better to state clearly that "federal research funds have not been available to investigate the materials damage effects of PM and its precursors since the mid-1980s." The costs associated with materials interactions with particulate matter could be better articulated. On page 9-119, in the second to last sentence, the statement could be made broader. For example: "Available data indicates that airborne particles can result in increases in the frequency of cleaning, maintenance, or replacement of exposed surfaces and materials, as well as reduced usefulness and enjoyment of injured materials (as is the case with stone monuments or dirty buildings)."

It was the Panel's judgment that with careful editing and revisions to address these general issues described here and the more specific issues presented in the individual comments it would be likely that the Panel could close on Chapter 9. Assuming that a revised version of this chapter and the Executive Summary, if there is to be one, are provided to the Panel by the

end of August, a teleconference meeting could be held in mid- to late September with the goal of completing the review of the AQCD for PM. As always, the CASAC PM Review Panel wishes the Agency well in this important endeavor.

Sincerely,

/Signed/

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***

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Also Member: SAB Board

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* Members of this CASAC 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) Panels for a particular criteria air pollutant.

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

This appendix contains the preliminary and/or final written review comments of the 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 both a full perspective and a range of individual views expressed by Panel 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.

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Dr. Ellis Cowling

[Note: Sent via e-mail to CASAC Chair Dr. Philip Hopke, members of the CASAC PM Review Panel, and the CASAC Designated Federal Officer (DFO) at 12:22 PM on August 2, 2004]

In general, I find substantial merit in this First Draft summary of CASAC comments. I believe these comments provide valuable guidance for NCEA's further efforts to provide a draft Air Quality Criteria Document for Particulate Matter that can be accepted in full by CASAC at its forthcoming conference call discussion — now tentatively scheduled for some time in mid September.

As befits my special particular role in CASAC, my major concerns about the AQCD for PM have to do with the need for a more balanced treatment in the AQCD for PM of "Welfare Effects," and the associated desirability of a "Secondary Standard" dealing with PM effects on various "Air-Quality Related Values."

These values include: 1) visibility impacts on human enjoyment of scenic vistas especially in national and state parks, 2) associated economic impacts on our tourism industries, 3) ecosystem responses to decreased solar radiation caused by regional haze, 4) increased atmospheric deposition of the nutrient and growth-altering substances in PM (including organic, oxidized, and reduced forms of nitrogen, sulfur, phosphorus, potassium, and the wide variety organic nutrients of fine and coarse aerosol particles, 5) direct effects on materials such as soiling of painted surfaces, exposed textile materials, etc., and 6) the need for greater concern during the next several decades about "smoke management" in light of the greatly increased risk of wild fires and the corresponding necessity for increased amounts of controlled burning of forests and natural areas in parks and other recreational areas.

Greater attention should be given in the AQCD to these "Air Quality Related Values" in rural as well as in urban areas.

Some of the many excellent and readily available photographs, tables, and figures should be added to the AQCD to illustrate and quantify such welfare effects as: 1) visibility impairment at scenic vistas and airports, 2) wild fire impacts on the aesthetic values of landscapes, 3) wildfire impacts on wildlife populations, 4) economic data on tourism impacts and smoke management costs and benefits, 5) the successes of urban areas that have adopted secondary standards for visibility impairment, and 6) changes in populations of aquatic invertebrates or fish that are induced by atmospheric deposition of the essential nutrient substances in the aerosols involved in cloud nucleation and precipitation processes.

With regard to ideas for inclusion in the summary of individual comments deriving from the CASC "Consultation on Methods for Measuring Coarse-Fraction Particulate Matter (PM_c) in Ambient Air, Based upon Performance Evaluation Studies Conducted by EPA," permit me to summarize the two points I made at near the end of this "Consultation" on Thursday July 22.

Point 1)

EPA (and many other federal research and monitoring organizations) need to guard against the tendency to allocate so much of the funds used in field measurement campaigns to “making careful measurements” and that inadequate funds are available for “scientific analysis and interpretation” to determine what the measurements really mean.

As described on pages 282-284 in the attachment to this E-mail message, these cautionary remarks about problems in field measurement programs were suggested originally by the late Glenn Cass, formerly of Cal Tech and later of Georgia Tech, on the basis of his career-long experience in various environmental monitoring programs — programs in which too much funding was allocated to “measurements” and too little to “analysis and interpretation” of the data. Please note on pages 283 and 284, the “Fifteen general and specific reasons why this happens” and the “Thirteen general and specific things that can be done about it!”

The reference for this published reviewed paper is: Cowling, E., and J. Nilsson. 1995. Acidification Research: Lessons from History and Visions of Environmental Futures. *Water Air and Soil Pollution* 85:279-292.

Please also note especially the suggestion in item 9 on page 284 about a “50:50 distribution” of funding allocations between “measurements” and “analysis and interpretation” of monitoring data rather than the (90:10 or 80:20 distribution) that is typical of many monitoring programs in EPA and other agencies.

But please also note that an even better suggestion was made by Mary Barber, former executive leader with the Ecological Society of America’s Executive, who opposed the “50:50 distribution” idea at a recent Whitehouse Conference on monitoring. Mary Barber insisted, and I agree with her, that it would be even more appropriate to distribute the funding into three rather than two categories of investments — with equal shares going to “measurements,” “analysis and interpretation,” and “outreach and extension of findings” to interested clientele and “customers” for the results of field measurement programs.

This problem is so commonplace — not only in this country but all over the world — that I commend these “lessons that are available to be learned” (and perhaps even the “15 reasons why this happens” and the “13 things to do about it”) for inclusion among the “comments from individual participants” in the CASAC Consultation on PM Measurement Methods.

Point 2)

EPA should also guard against the tendency to give undue emphasis to “Data Quality Objectives” in the selection and evaluation of instruments and subsequent implementation of field measurement programs to the exclusion of concern about “Science Quality Objectives” and “Policy Relevancy Objectives.”

Experience within the Southern Oxidants Study and other large-scale field measurement campaigns have demonstrated repeatedly that undue emphasis on “Data Quality Objectives” often leads to:

- 1) Serious lack of attention to the scientific hypotheses and assumptions that are inherent in any choice of scientific instruments, the appropriateness of the ground-based sites or aircraft platforms on which the instruments are mounted, the skills of the instrument operators, the data processing and data-display programs used, and especially the scientific quality of the conclusions and statements of findings that are drawn from analysis and interpretation of the measurements that are made; and

2) Equally serious lack of attention to the policy relevancy of the measurements being made — relevancy to the general or specific enhancements of environmental protection that are the *raison de etre* of the public health or public welfare concerns that led to the decision to establish a monitoring program or undertake a field measurements campaign in the first place.

In this latter connection, permit me also to call attention to the “Guidelines for the Formulation of Scientific Findings to be Used for Policy Purposes” which were developed originally by the NAPAP Oversight Review Board led by Milton Russell. Please find attached to this E-mail message, an electronic version of these Guidelines which we have adopted and very slightly adapted for use in formulating policy relevant scientific findings in the Southern Oxidants Study.

The original version of these Guidelines was published as Appendix III of the April 1999 Report titled “The Experience and Legacy of NAPAP.” This was a Report to the Joint Chairs Council of the Interagency Task Force on Acidic Deposition of the Oversight Review Board (ORB) of the National Acid Precipitation Assessment Program.

As indicated in Appendix III:

“The following guidelines in the form of checklist questions were developed by the ORB to assist scientists in formulating presentations of research results to be used in policy decision processes. These guidelines may have broader utility in other programs at the interface of science and public policy and are presented here with that potential use in mind.”

These guidelines may also be of value as part of the “communication of individual comments” from the CASAC Consultation on PM Measurement Methods.

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Dr. Frederick J. Miller

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July 21, 2004

Chapter 7

General Comments

The fourth version of Chapter 7 on the toxicology of PM in humans and laboratory animals represents an overall improvement from the third draft version. The Chapter's Integrative Summary section is still missing various important points such as the fact that CAPs do not concentrate the gaseous phase and that dosimetry modeling predictions indicate many of the animal and some of the human studies used doses that call into question the relevance of the results to real world exposures.

The Appendix 7A on rat to human dose extrapolation provides valuable information for putting into perspective the relationship between various exposure levels and instillation doses used in animal studies relative to the comparable kinds of exposure levels or doses that would be needed in humans. Unfortunately, some of these examples have failed to find their way into Chapter 7. Specifically, there is no inclusion in the new Section 7 of Chapter 7 that relates to the intratracheal instillation studies for the Utah Valley dust used in both human and animal experiments. This is a major omission that needs to be corrected. To their credit, the authors have included in Section 7 examples of inhalation with CAPs studies as well as in vitro experiments and the relevant kinds of interspecies dosimetric comparisons that enable judgments to be made about the potential extrapolation of the effects seen in the animal studies.

The reason the instillation studies need to be also covered is that there is a clear pointing out in Appendix 7A that the authors of the human and animal studies using the Utah Valley dust incorrectly reported what would be equivalent kinds of exposures or typical community exposures associated with their instillation doses. For example, instead of a single day or up to one week of exposure for the human instilled doses as stated by Ghio and Devlin, exposures would need to be on the order of two months. Since EPA has placed great weight on the apparent similarity of results between studies with the Utah Valley dust in both animals and humans, it is imperative that Chapter 7 correctly portray the relevance of these instilled doses to real world ambient exposures. Similarly, while Table 7-15 is a useful addition to the new Section 7.7, the discussion in the text surrounding this Table still does not do enough to put the in vitro doses into perspective. Doses are reported in terms of nanograms per cell estimated from information in the publications, and most readers would interpret these doses as being low rather than high. However, taking into account the density of the cells on the plates and the mass associated with a single particle, the lowest doses reported still involve each cell seeing anywhere from about 25 to 400 particles, which is not a small dose. That being said, Table 7-15 helps to establish a dose response relationship for the effects of PM on alveolar macrophage phagocytosis.

A new Appendix on ambient bioaerosols has been added to Chapter 7 and appears as Appendix 7B. This Appendix inundates the reader with information about fungi, bacteria, viruses, pollens, plant fragments, etc. Unfortunately most of the information indicates the quantities that are present in the air in various locations and seldom presents effects of this material on humans or animals. If the Agency is presenting the information on ambient

bioaerosols as part of a case for the interaction or synergism of these materials with ambient PM, the authors have an obligation to report effects seen in animals or humans with these materials and at what levels these effects are seen. Failure to do so provides an open end for an argument of their importance when such is probably not the case. For example, Section 7B.2.1 describes atmospheric levels of cellulose and reports them to be typically less than $1 \mu\text{g}/\text{m}^3$ in the air and in some locations up to around $6 \mu\text{g}/\text{m}^3$, yet there is no discussion of studies that have been conducted on the effects of cellulose in animals or humans. I have provided about 25 references for studies where cellulose exposures to animals or humans were in the mg/m^3 or more range seeing very little if any effects of the material on human health outcomes. This disparity in coverage is of concern and needs to be rectified. On a broader basis, the treatment of bioaerosols in the interpretative summary of PM toxicological findings in Section 7.9 falls short of delivering a punch line in relationship to the constituents of PM that EPA would propose to regulate in any standards that are revised or added.

Specific Comments

- p. 7-3, l. 17 The authors refer to analyses contained in Appendix 7A. Some of the highlights of those findings should be presented in the main body of the chapter, perhaps to the extent of a page of description of the more notable results. Otherwise, most readers will skip the Appendix and not really be informed of the salient points that the Appendix makes relative to the interpretability of several studies that EPA has deemed key for concerns about the potential effects of PM exposure to humans.
- p. 7-4, ¶ 1 The authors continue to fail to point out that CAPs systems do not allow for concentrating any gaseous components. This means that potential interactions present in the ambient atmosphere are not captured in the same proportionality via the CAPs studies. This point should be captured in the interpretive summary for Chapter 7.
- p. 7-28 In Section 7.2.3, there has been no attempt to bring in information from the extrapolation appendix to put the ROFA exposures into perspective. Based upon the extensive calculations that were done by EPA for Appendix 7A, this certainly could and should be done because it will clearly demonstrate that most of these studies are not providing information relevant to anywhere near real world exposure levels.
- p. 7-45, l. 15 The study by Bouthillier used resuspended Ottawa UAP ambient PM on the size of 4–5 μm in MMAD. As Appendix 7A shows (Figure 7A-4) only about 60% of the material would have been inhalable and most of this would have been trapped in the nose. Whether this supports or does not support a lack of effects seen in the study is not as important as the need to put some of these kinds of study results into perspective from a dose viewpoint.
- p. 7-49, last ¶ The point made here relative to the fact that the high exposures contained in many of the studies may overwhelm lower dose mechanisms and that the high dose instillation studies may actually produce different effects

on the lung than inhalation exposures at lower concentrations or doses is an important point. However, this point does not make its way to the interpretive summary section of Chapter 7 (i.e., Section 7.9), but it should.

- p. 7-50, ¶ 2 This discussion of the properties of ROFA and the metal content that leads to toxicity is a better description of the body of evidence around ROFA than is contained in Section 7.9 on p. 7-24 where ROFA effects attribution are discussed. Consider reworking of the material on p. 7-24 to better reflect that contained on p. 7-50.
- p. 7-118 The discussion of potential importance of particle charge may be somewhat superfluous because ambient aerosols to which humans are exposed have come to Boltzman equilibrium. Charge would only be important for freshly generated material such as in a workplace atmosphere.
- p. 7-123, l. 9 This paragraph describing the Churg et al. study is excessive in length. The same points could be made in a shorter paragraph.
- p. 7-126, l. 1 In the final version of this chapter, EPA should make an attempt to not have major sections begin on a separate page but rather conserve space by having them flow immediately from the conclusion of the preceding section.
- p. 7-126, l. 14 The statement that the laboratory generated particles may be of limited value because of uncertainties in extrapolating between laboratory generated and ambient particles seems to have escaped comment in earlier versions of this chapter. This particular sentence is too strong a statement in the view of this reviewer since dosimetry models allow for an interspecies dosimetric adjustment of any findings. The more relevant point the authors were probably trying to convey was that studies of individual particles may not provide the overall picture compared to the complex mixture of exposures that occur in urban aerosols.
- p. 7-155, l. 18 While the Ottawa UAP and ROFA studies are at unrealistic exposure levels and probably don't have much relevance for evaluating current ambient PM levels, the authors should note that these studies were conducted in healthy animals. Thus, the potential certainly exists for lower exposures in compromised animal models to show effects at much lower exposure levels.
- p. 7-160, l. 4 It is incorrect to refer to instilled material as exposure concentrations. It was an administered dose of 3mg/kg in the particular sentence. The entire Chapter 7 should be checked for instances of inappropriate wording of exposure concentration when really the correct terminology would be administered dose.
- p. 7-164, l. 25 Would suggest extending this sentence instead of stopping at "are identical" to state "are identical because of variations in individual

breathing patterns, lung anatomy, and particle deposition fractions.

p. 7-166, l. 10

The paragraph is a good example of how dosimetry models can be used to make interspecies comparisons of potential effects after adjusting for dose differences. However, in this particular paragraph, the authors should note that their statements about the $\mu\text{g}/\text{m}^2$ of delivered material are related only to the insoluble part of PM since the dosimetry model upon which these doses were calculated considers only insoluble particulate matter. Thus, a caveat should be included to indicate not only this but that the accounting of the soluble fraction could lead to a more complex statement of potential differences between rats and humans. Moreover, in this paragraph, the authors should be more cautious about ascribing significance to a 60–500% increase in PMNs in the rat compared to about a 40-fold lower dose (mass/m^2) yielding a 267% increase in humans. The basal level for the percent increase greatly influences the calculated percent increase

p. 7-167, l. 26

Please clarify if the statement “soluble and insoluble components” in parenthesis is made to imply $\text{PM}_{2.5}$ was the soluble and PM_{10} the insoluble. If this was what was intended, it is an incorrect characterization because both the fine and coarse modes contain soluble as well as insoluble components although there is a greater percentage of constituents of the fine mode that are soluble..

p. 7-168, l. 25

It should be 500 μg instead of 500 ug.

p. 7-169, l. 2

Unless the abbreviation for right angle light scatter is used subsequently, it should be deleted.

p. 7-169, l. 3–4

Again, μg should be used in place of ug.

p. 7-170

Table 7-15 provides an interesting set of information concerning phagocytosis effects of particulates in humans and rodents. The title of table could probably be shortened to something such as “Interspecies Comparisons of Particle Effects on Alveolar Macrophage Phagocytosis”. For the Goldsmith et al. study entry with 0.4 as the estimated dose per cell in terms of nanograms, the estimated percent filling of 140% is an impossible value and should either be deleted or asterisked to note that it is not possible to obtain such a value. In the Van Eden portion of the table, there appears to have been a data entry for the 0.02 ng value where the as percent filling is 2.121. If this is indeed computed, it certainly should be rolled back to 2.1%. However, there is no data entry with 0.2 ng, and this value for percent estimated of cell filling needs to be inserted.

p. 7-171, l. 7–8

The units here should be ng/cell not mg/cell if the entries in Table 7-15 are indeed in units of nanograms per cell.

p. 7-181

Add an “s” to sampler.

- p. 7-182, l. 23 The authors state that the studies they have discussed provide strong new evidence indicative of ambient PM having mutagenic properties. To this reviewer, this is an overstatement of the body of data and the interpretation of such, particularly since most of the work involved transform cells whereas normal human epithelial and other lung cells are not easily mutated.
- p. 7-183, l. 21 Insert a comma after assay and remove the left-hand parenthesis in front of Houk putting it in front of the year and also removing the comma after al.
- p. 7-186, l. 3 This reviewer would hardly call studies conducted in the late 1980s as more recent studies.
- p. 7-200, l. 5 The authors use the words extensive credible evidence relative to the biologic plausibility and potential mechanisms relating to the ability of ambient PM to be associated with lung cancer. This seems like an overstatement and a better characterization would be that they provide some credible evidence.
- p. 7-202, l. 1 In various places, the authors have indicated that rats clear particles faster than humans and this is the reason for the higher doses. While this is indeed the case relative to clearance, rats also have a lower deposition fraction than do humans for most particle sizes, which in itself also leads to higher exposure levels being needed in animals compared to humans. This should be pointed out here and in various other places in Chapter 7 and in Appendix 7A.
- p. 7-203, l. 23 The assumption by Ghio and Devlin of an average ventilation of 15L/min is not supportable either from EPA's documentation of typical activity patterns and ventilation rates nor from the published literature.
- p. 7-203, l. 27 Why have the authors of Chapter 7 not put the statements by Ghio and Devlin of comparable exposure levels into perspective as was done in the extrapolation appendix on page 7A-45 where it was clearly shown that between 44 and 65 days would be required for a person to deposit the instilled dose that was used in these studies? An integration of the results from the extrapolation appendix have not found their way into the interpretations in Chapter 7. This needs to be corrected.
- p. 7-206, l. 25 The caveat about relevance of ROFA studies to real world exposures is quite weak here compared to what is expressed on p. 7-161. The tone in the earlier sections is what should be conveyed in Section 7.9.
- p. 7-210, l. 3 Strike "previously".
- p. 7-211, l. 2 Insert "of" after production.

Appendix 7A

Specific Comments

Table of Contents

In the Table of Contents, Multiple Path Particle Deposition Model should be referred to as Multiple Path Particle Dosimetry Model.

Entry 7A.5 Should read Dosimetric “Calculations” instead of “Calculation”.

Figures/Figure Legends

In the list of figures and in the figure legends themselves, suggest replacing Human with Humans and Rats for Rat.

Text

- p. 7A-3, l. 1 Remove the hyphen in inter-subject.
- p. 7A-3, l. 12 Suggest rewording to be “in a lung region may be expressed as”.
- p. 7A-4, l. 1 Insert a comma after comparisons.
- p. 7A-5, l. 14 Should be exposures not exposure.
- p. 7A-6, l. 20, 22 Again, deposition should be replaced by dosimetry in the definition of multiple path particle dosimetry model.
- p. 7A-6, l. 24 It should be RIVM not RIM.
- p. 7A-8, l. 5 Should be macrophages not macrophage.
- p. 7A-8, l. 17 As stated, the sentence after the i.e. is incorrect. What the authors are probably intending to say is that mucus itself is not reabsorbed in the respiratory tract. However, mucus secreting cells are located throughout the conducting airways and there is secretion at every level, even though there is reabsorption of water, otherwise there would be total occlusion of the trachea with a cumulative flow of the secretions from the lower respiratory tract.
- p. 7A-13 In Panel A where mass is presented, what does the number 100 in parenthesis stand for under the title of Resuspended?
- p. 7A-14 Insert “of” after distribution.
- p. 7A-15, l. 5 Suggest adding in parentheses reference back to Chapter 6 where it was noted that neither the ICRP nor the MPPD model should be used for particles < .01 due to not taking into account the effective actual dispersion of particles that size.
- p. 7A-18, l. 7 In the section on retention, it would be worth noting that clearance is indirectly represented in the curves because you are examining the amount retained and therefore the amount compared to the previous time is the amount that was actually cleared. Some readers may find it

- confusing to be interchanging clearance with retention.
- p. 7A-19 The legend for the figures is incorrect in that it does not delineate the postexposure time in hours only represents the value after 1 hour such that m/m_0 for the first hour represents the rise in concentration during the hour of exposure. The figure needs to be corrected.
- p. 7A-20, l. 2–3 The figure contains both tracheobronchial and alveolar data so the sentence here should be TB or A region in both places where currently only TB region is specified.
- p. 7A-23 Delete “of” in the last line of the figure legend.
- p. 7A-25 This material does not need to be a separate subsection. It could be combined with the section on normalizing factors and a new title given. This is particularly the case since no text is really contained with the section and it is merely a summary table.
- Section 7A.4.6
- p. 7A-26 For the entire section on comparing rats to humans, the authors should make clear that the various scenarios they have modeled invokes the assumption that “a particle is a particle” and that the dose mass can be aggregated over multiple size modes. In reality, it is extremely unlikely that this assumption could be met since the PM is comprised of many types of particles each having their own size distribution. Rather the authors should make it very clear that the kinds of calculations presented are for illustration of how you would go about computing dose if definitive information on speciation, size distribution, etc. were available such as may be forthcoming from the EPA PM supersite monitoring efforts.
- Section 7A.5
- p. 7A-27 In the first sentence after equation 11b, strike “the variety of”.
- p. 7A-27 For the example where the EqER ranges from 0.9 to 5.5, suggest putting in parentheses, “see first section of Table 7A-7a” to help orient the reader.
- p. 7A-30 For the EqER values contained here, it would help the reader to locate the areas of the table if Table 7A-7a and 7b had roman numeral sections added to them such as I, II, III, IV, and V so for example, deposited mass might be I, retained mass in the TB might be II, surface area of particles retained in the alveolar would be III, etc.
- p. 7A-31 Add “of” after values.
- p. 7A-37 On last line of page, insert “of” after 10 years.
- p. 7A-42, l. 10 Insert a comma after species.
- p. 7A-45, l. 10 Isn’t the point being made using insoluble particles that the computations of Ghio and Devlin relative to the amount of time that a person would have to be exposed is incorrect? Whether the appropriate dose represented the soluble or insoluble fraction is not really the issue. The authors could illustrate this difference by adding an additional sentence

wherein they only use 20% but considered it insoluble just to see what kind of time period exposures would have to be to get the dose that Ghio and Devlin instilled.

- p. 7A-46, l. 16 Insert “to” after equal.
- p. 7A-50, l. 21 Should be overload is “affected”.
- p. 7A-54, l. 27 The statement concerning not being able to simulate chronic retention in humans except under conditions of overload for rats is not correct. This statement is only true for high exposure levels in humans. However, ambient exposures of the 10 to 20 $\mu\text{g}/\text{m}^3$ that are being considered as part of the PM_{10} revisions should be able to be estimated by comparable rat equivalent exposure levels.
- p. 7A-54, l. 30 The thrust of the ILSI Workshop (*Inhal. Toxicol.* Vol. 12, 2000) makes it quite clear that overload of poorly soluble particles is dependent on coexistent active inflammation and cell proliferation, which is a high dose phenomenon, and that effects such as lung cancer would not be expected at typical ambient exposure levels. The same could be said for various noncancer effects. The authors are making a significant and speculative “leap of faith” that rats in lung overload may simulate the response of susceptible or impaired humans. Since this topic is not treated in the main body of the chapter, which it should be if there was any evidence for the speculation made by the authors, this material should be omitted or substantially toned down.
- p. 7A-56, l. 4 It should be “affected” by PM.
- p. 7A-58, l. 25 I believe the authors are intending to used criticized instead of critiqued.
- p. 7A-59 The Conclusion section should contain several additional bullets that specifically relate to the instillation studies of the Utah Valley dust and the disparity in results compared to the authors as far as equivalent doses. In addition, the CAP studies and their closer similarity for extrapolation purposes should be highlighted.

Appendix 7B

Specific Comments

- p. 7B-9 The Celenza study did not characterize the concentration of pollen or any size distribution. So how can the author contend that following a thunderstorm the increase in ER visits is due to pollen levels? This reviewer questions the value of including this study. If one of the publications cited on p. 7B-14 concerning allergens following thunderstorm and asthma-like effects has quantitative data on concentrations or particle sizes, this reviewer would suggest one of these

references be included in the table rather than the Celenza publication.

- p. 7B-9 The title of the table is Respiratory Effects of Pollen/Fungi in PM Exposures. However, there is little if any information in the table relating to the PM exposures so that the table could just as well be labeled Respiratory Effects of Pollen/Fungi and Ozone or Respiratory Effects of Pollen/Fungi and Sulfur Dioxide, etc. The point being that the table more reasonably should be labeled Respiratory Effects of Pollen/Fungi and Air Pollution.
- p. 7B-10 In an effort to be complete, the authors have gone overboard by including the Piecková and Kunová (2002) study. This experiment did not measure concentration or particle size of any of the filamentous fungi in their in vitro study of chicken tracheal rings. Yet the report is that it stopped tracheal ciliary movement. If such conditions were prevailing in humans, the epidemiology would be a whole lot clearer than it is. This study adds little value in the opinion of this reviewer and should be deleted.
- p. 7B-12 Section 7B.2.1 on atmospheric levels of cellulose and other plant debris markers indicate that the cellulose levels, while being in some locations a significant constituent of PM, are themselves only a few $\mu\text{g}/\text{m}^3$. In contrast to this, the toxicological studies on cellulose in the mg/m^3 range show very limited responses if any. These studies have been done in both animals and humans. If the agency is invoking the contribution of bioaerosols in an interactive form with PM, then there is an obligation to put the known effects of bioaerosols into perspective. This has not been done. To assist the agency relative to cellulose, a number of citations are provided that have studied the effects of cellulose in animals or humans.

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- Love, R. G., Smith, T. A., Gurr, D., Soutar, C. A., Scarisbrick, D. A., and Seaton, A. (1988). Respiratory and allergic symptoms in wool textile workers. *Br. J. Ind. Med.* 45, 727–741.
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- Pauly, J. L., Allaart, H. A., Rodriguez, M. I., and Streck, R. J. (1995). Fibers released from cigarette filters: an additional health risk to the smoker. *Cancer Res.* 55, 253–258.
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Warheit, D. B., Reed, K. L., Pinkerton, K. E., and Webb, T. R. (2002). Biodegradability of inhaled p-aramid respirable fiber-shaped particulates (RFP): mechanisms of RFP shortening and evidence of reversibility of pulmonary lesions. *Toxicol. Lett.* 127, 259–267.

p. 7B-14, l. 8 Delete “which” and replace it with “that” or else insert a comma after “evidence”.

p. 7B-19, l. 3 The 3 on O should be a subscript, not a superscript.

p. 7B-20, l. 4 Do the authors really mean macro organisms or do they mean micro organisms?

p. 7-24, l. 1 The study by Vogelzang describes effects of endotoxin related to decline in pulmonary function obtained by regression analysis. There is no discussion of what variables were controlled for in the regression and this should be noted to insure that other variable were controlled for.

p. 7B-24, l21 The Zock study showed a decline in FVE1 of 3% during a shift a potato processing plant. This decline may have been statistically significant but certainly doesn't meet the American Thoracic Society criteria of clinically significant change. The question arises as to whether Zock looked at multiple days and found the same decline or was this a one time event?

p. 7B-28, l. 15 Check the $\pm 147\text{ng}/\text{m}^3$ for fidelity with the original publication. If this number is indeed correct, it shows significant lack of control of the experiment and certainly in this reviewer's mind draws into the question the results.

p. 7B-29, l. 20 The results of the phadioatop test being statistically significant when analyzed for age represents a post hoc analysis and can only be considered as exploratory. It is troubling to this reviewer that many of the studies appear to analyze for every possible combination and are not based upon a testable hypothesis.

Chapter 8

Specific Comments

p. 8-217, l. 5 The description of the results for which models would be selected using the BIC is misleading. As described in public comments (Moolgavkar, p. 8 at the bottom), the authors should specifically state that the AIC and BIC only both give a RR of 1.05 when models that included PM were included as a covariate. Otherwise the top 25 models had under AIC an estimated RR of 1.05 and under BIC an estimated RR of 1.015 when the Bayesian Model Averaging approach was used. This is a much different

depiction of the results compared to the way the authors of Chapter 8 described this study. Any changes should also find their way to Chapter 9.

- p. 8-217, l. 18 It should be $p < 0.05$ not $p \leq 0.05$.
- p. 8-219, l. 19 The discussion indicates that the GAM-default vs. GAM-stringent analyses for the most part do not lead to significant changes in the risk estimates. Later on in the synthesis part of the chapter, it is argued that the multi city studies have greater precision. Yet there is no note that in Table 8-36 the NMMAPs 90 city study went from being statistically significant for the PM effect in the GAM-default analysis compared to the GAM-stringent analysis wherein the effects of PM₁₀ were no longer significant. To this reviewer, this is a striking discrepancy of the interpretation of the overall body of work given the reliance later on multi city studies being viewed as more precise and carrying greater weight. That this loss in significance may be due to a biased downward value in the standard error may be part of the explanation for this but on the next page it is stated that the GLM with natural splines that was used in the reanalysis study, which I presume is the GLM entry in Table 8-36, does not have a bias of the standard error; yet for this GLM analysis of the NMMAPs studies, the PM₁₀ effect is still not statistically significant. This situation is further confused by the plot of the NMMAPs data in Figure 8-15 where the error bars around it show that all three analyses methods are statistically significant. So which is correct, and what is this reviewer missing?
- p. 8-223, l. 30 Shouldn't it be p-values > 0.05 not > 0.5 ? And how does this compare with the statement on page 8-228 by the HEI committee that the effect estimates were quantitatively smaller in the original studies but that the overall effect of PM₁₀ on mortality remained.
- p. 8-274, l. 21 Insert "than" after "less" so it should read "scale of less than 100 miles".
- p. 8-281 The authors of the epidemiology chapter should give consideration to shortening the titles of the various tables and figures. For example, the title to Table 8-40 is typical of excess wording.
- p. 8-305, l. 5 The statement here implies that the model used by Pope included interaction terms for smoking and pollution versus not smoking and pollution such that the effects of smoking as a main factor could be eliminated and yet the potential interaction with pollution be detected. Were these terms indeed included in the followup analysis of the ACS study?
- p. 8-306, l. 25 The discussion here of individual vs. population threshold is somewhat masking the issue relative to the Clean Air Act. The Clean Air Act does not require that every single member of the population be protected but rather sensitive subgroups of the population. Thus, the concept of threshold is still relevant even though it is a difficult task to identify

whether a threshold exists.

p. 8-307, l. 26

As this reviewer has previously noted, the grid search involving $5 \mu\text{m}/\text{m}^3$ increments is too coarse a grid in relationship to the fine particle standard of $15 \mu\text{m}/\text{m}^3$. The increments represented 33% of the standard and a realistic search should have had much finer grid increments on the order of $1\text{--}2 \mu\text{m}/\text{m}^3$. The grid size is also a function of the roughness of the response surface being examined. Either the authors of this chapter should acknowledge these concerns or else provide information that refutes it.

p. 8-308, l. 14

How was the hypothesis of linearity more formally examined using AIC values across models? Was a statistical test applied to distinguish if two models were significantly different? The question of changes in the AIC for really being interpretive is analogous to the results of an analysis of variance where Bernhard showed that an F value had to be four times the computed value before one could really discuss that statistical significance was at a lower level of probability than what had been stated a priori. In short, a couple of sentences should be added here explaining how the AIC was used from a statistical viewpoint.

Chapter 9

General Comments

Given that CASAC provided consultation to the Agency and basically endorsed the outline of the integrated synthesis chapter, it would be hard to fault the Agency for the structure of the chapter. That being said, there is considerable imbalance between the sections that address new information on the broader set of questions that are the section titles for 9.2.1, 9.2.2, 9.2.3, etc. Not all of this imbalance is due to the amount of additional information that has been developed since the 1996 review, but may be due to different subsection authorship and writing style. Common throughout Chapter 9 is an excessive use of adjectives such as “considerable”, “strong”, “very”, “extensive”, etc. such that the reader gets the impression that a harder sell is being made than what may be warranted by the data contained in the first 8 chapters of the Criteria Document.

The integrated synthesis contains a number of technical errors in bringing forward material from the other chapters, some of which are noted in my Specific Comments. The authors of Chapters 8 and 9 have continued to not address the concern I expressed relative to the Brunekreef (1997) study purporting a reduction in life time expectancy due to PM exposure increase of $10 \mu\text{g}/\text{m}^3$ and the calculation of a reduction of about 1.3 years for the entire population’s life expectancy at age 25 using 1969-1971 life table data. This calculation needs to be redone using a life table not 30 years out of date. Moreover, the vastness of this decrease is clearly not detected in the few long term mortality epidemiology studies that have been conducted. This is but one example of where CASAC or public comments on technical matters have largely been ignored in further drafts of CD chapters.

I still get a sense of “selectivity” in Chapter 9 compared to an analysis of “here is what we know now about PM health effects in 2004 compared to what we knew in 1996 and here are areas of PM effect analyses where we honestly can’t say what is going on”.

I would have thought that the integrated synthesis would focus more within the sections on whether the information sheds new light as to the level of the standard, the averaging time, the value, etc. As an example, the section on the discussion of lag times (9.2.2.2.4) would benefit from a consideration of a moving average for a standard since the results for the various lag times can vary considerably, although the authors make the point that a greater span of time should provide a more stable estimate of the overall magnitude of potential PM effects and that shorter lags may underestimate the PM effect.

Some consistency in the structure of each of the subsections should be imparted by a technical editor. Currently, some sections include references while others do not, and the bottom line of the conclusions on the incremental information provided by studies since the 1996 review is not always clear. In addition, the bottom line is evident in some of the sections but not in others.

Specific Comments

- p. 9-1, l. 23 Suggest adding at the end of the sentence “or to establish a new standard for PM_{10-2.5}”.
- p. 9-13, l. 10 Add to this list the anatomy of the respiratory tract of the individual.
- p. 9-19, l. 7 Insert PM exposure after short-term.
- p. 9-13, l. 14 It should be PM_{10-2.5} in this sentence.
- p. 9-24, l. 10 Most of the text on this page is redundant with the previous page. The percent increased risk discussion should be combined with the discussion on the previous page about the degree of association be it positive or negative and the extent of statistical significance of various effects with the three PM indicator variables.
- p. 9-35, l. 7 For the analysis discussion in Section 8.4.5.2 and brought forward to Chapter 9, the creation of six 1-in-6 day data sets and the resulting inconsistency of PM mortality associations appears to be used as an argument for restricting analyses to those that only have data for every day and do not attempt to do any extrapolation of values based upon atmospheric models or whatever. This is a potentially very important finding because EPA should assess how many studies used 1 and 6-day values compared to those that have every day analyses and determine the overall magnitude of effect when the data sets are more complete. The bottom line is that the 1-in-6 day sampling pattern is adding uncertainty to the PM effects and represents the kind of uncertainty addressed by Koop and Tole (J. Environ. Econ. Management 47, 30–54, 2004). In addition, the sites for which the data are available every day could be used informatively to establish the lag time or basically the averaging time which is one of the important factors that has to be considered in the development of any PM standard.

- p. 9-46, l. 8 This reviewer is under the impression that the broader toxicologic community views the monocrotaline treated rat model as not very useful for studying the effects of PM due to the severity of the state of the animals before being challenged with PM exposures as well as the fact that the model acutely tries to develop in animals what is a chronic process in humans.
- p. 9-50, l. 27 Why restrict the discussion here to TB cell exposures? A more logical statement is lower respiratory tract cellular exposures as instillation clearly allows for particles to be delivered throughout the lower respiratory tract, albeit to a greater extent of variability than by inhalation.
- p. 9-53 The same cautions concerning interpretations of the results shown in Table 9-4 are warranted in the integrated synthesis chapter as this reviewer has conveyed for the original presentation of the information in Chapter 7.
- p. 9-54, l. 5 This paragraph needs to be put in perspective relative to the actual number of particles that a given cell would be exposed to because the in vitro doses are misleading in that they correspond to tens to hundreds of particles per cell and thus are still in the extremely high dose mode.
- p. 9-54, l. 30 The study by Ulrich et al. used such high instillation doses that the results of showing an increase in plasma fibrinogen by Ottawa UAP are an absolutely high dose phenomenon and to this reviewer are not worthy of being included in the integrated synthesis chapter.
- p. 9-55, l. 4 The same comment as above can be attributed to the ROFA studies involving inhalation of 10–15 mg/m³.
- p. 9-55, l. 14 The characterization of the Ottawa UAP study in rabbits is incorrect in saying that the material caused increases in atherosclerotic lesions. As described in Chapter 7 on page 156, the study showed a progression of atherosclerotic lesions and not an increased number of them.
- p. 9-57, l. 2 Delete the first “in” that appears before BAL.
- p. 9-57, l. 16 Again, the integrated synthesis does not put the in vitro studies into perspective relative to number of particles that each cell would see. Calculations show that these numbers would range in the tens to many hundreds of particles per cell and clearly still represent a high dose phenomenon.
- p. 9-58, l. 1 Delete “strong”. What is the criteria by which one would use the adjective strong in this instance?
- p. 9-60, l. 28 We hardly need the new studies to know that some types of particles are more toxic than others. This understanding has been present for at least 30 years.

- p. 9-61, l. 20 Change “dosimetric” to “dose metric”.
- p. 9-76, l. 23 In this paragraph, the authors should make clear that they are talking about aerodynamic diameters at least with respect to the 1–2 μm particles; i.e., the density of the particle needs to be taken into account via the aerodynamic diameter.
- p. 9-77, l. 9 Ozone is a bad example to describe toxic material in the particle bound water aspect of a droplet given the extreme insolubility of ozone in water.
- p. 9-77, l. 17 This paragraph somewhat overstates that trends in deposition and patterns of deposition seen in diseased or compromised lungs in that the experimental studies have not used a wide range of particle sizes, and the authors should indicate the size range for which these statements are considered to be appropriate.
- p. 9-78, l. 19 Again, remove ozone from this list of agents.
- p. 9-78 Delete “the” at the end of the line. In addition, the statement that they likely contribute to some types of ambient PM health effects exposure is probably an overstatement given the description of effects and the concentrations of these bioaerosols needed to produce any changes (see Appendix 7B). Such is at least the case for cellulose given that ambient levels are typically only a few $\mu\text{g}/\text{m}^3$ whereas effect studies have used mg/m^3 quantities and seen very little changes in health outcome in either animals or humans.
- p. 9-83, l. 18 Once again, the authors of the integrated summary have not brought forward the results from Appendix 7B which show that the instillation doses are not equivalent to higher level exposure concentrations that could be experienced in the time frame for which the original authors contend. Rather, the doses correspond to 6–9 weeks of elevated exposure and as a result are not reflective of the community-wide exposures that individuals would be expected to receive.
- p. 9-84, l. 28 Exposures over several weeks to PM_{10} is an incorrect statement compared to requiring 6 to 9 weeks of exposure as determined on p. 7A-45 of the extrapolation appendix.
- p. 9-85, l. 12 Perhaps a more accurate representation of the extent to which exposures of humans at higher ambient levels compare with doses in exposures used in toxicological studies would be to indicate on this line instead of “are often not necessarily” changed to “are sometimes not necessarily”.
- p. 9-85, l. 31 Again, delete ozone from the list.
- p. 9-90, l. 14 The reference to the figure whereby dose is stated on a per kg bodyweight basis being much higher can’t really be determined from the figure since it merely relates to the inhalation rate as a function of age. If deposition rates are different in children than adults, this would be a

major driver in dose comparisons between children and adults. The statement is made later in the paragraph that the discrepancy is even greater when viewed on a per lung surface area basis. This is indeed correct, but why not show this kind of data in a figure rather than the inhalation rates from the Layton (1993) publication?

p. 9-99, l. 19

It seems inappropriate to this reviewer to characterize childhood asthma as a less serious condition compared to other health outcomes later in life.

p. 9-102, l. 8

The entire section on welfare effects is interesting reading but really does not come down to any bottom line relative to potential changes of any existing welfare standards or addition of new ones. Aside from the obvious positive impact on visibility by reduction of fine particles, the rest of the synthesis really does not provide a punch line as to the benefits that could most likely be achieved with fine mode PM reductions. The variability between air sheds and ecosystems and the amount of N_r doesn't seem to support the conclusion that one might expect — namely that reduction in N_r would result in an improvement in the ecosystem.

Mr. Richard L. Poirot

Chapter 9 Comments, R. Poirot

Overall, this is a very good first shot at an inherently difficult target. I don't think major substantive changes should be required to finish this chapter and finalize the CD.

9.2.1: The first question considers the continuing distinction between fine & coarse particles, provides strong support for such a distinction, and in several cases (for example, new information on characteristics of particles in the “intermodal” – 1-2.5 um – size range), further strengthens the selection of 2.5 um as the division point. By contrast, discussion or additional justification of the 10 um upper cut-point for “coarse particles” seems notably absent. It's been several decades since the 10 um cut-point was carefully considered, and revisiting this decision seems especially important if 2.5 is now firmly established as the lower cut-point – thereby excluding the fine tail of the coarse mode from the newly defined “PM_{10-2.5}” category, which will also exclude the coarse tail (& in some cases most of the whole dog) of the coarse mode particles from consideration. There are several indications throughout the chapter that crustal particles (which typically compose the majority of the coarse mass) appear to be uniquely not associated with adverse health effects (and I think generally the mass – without regard to the composition – has virtually no relevance to effects on environment). Yet we appear poised to develop and implement costly new ambient measurement programs specifically focused on quantifying the mass of particles in the PM_{10-2.5} size range. Is this wise?

p. 9-5, lines 19-20: Could delete “re” from “resuspended”, delete “in dry dusty areas”, and delete “in cities”. The fine tail of coarse-mode suspended soil particles exists in humid areas too, and since coarse mode particles are less abundantly emitted in humid areas, their presence there often originates elsewhere, such that a proportionately larger fraction of larger coarse-mode particles has been removed during transport. Fine (but coarse-mode) sea salt particles and their derivatives exist everywhere near oceans (not just cities) and are often observed many hundreds of miles inland.

p. 9.7, line 1: ditto.

9.2.1.2.3: When using terms like “fraction of inhaled particles”, “most accumulation mode particles” and “fractional deposition”, I assume you intend “fraction by number” and not by mass? If this is the case – or not – it would be helpful to state clearly, since few other discussion sections relate specifically to particle count. Possibly it could be informative to comment on the associated mass fractions (in Figure 9-4, for example).

pp. 9-21&22, Figures 9-5 and 9-6: Are excellent data visualization & communication applications! I don't suppose there would be any easy way to distinguish between those studies that included 1, 2, 3, 4,... different PM-size ranges and/or effects metrics? Also, here and in following pages, is it absolutely necessary to use different units (i.e. per 50 ug/m³ for PM₁₀ vs. per 25 ug/m³ for PM_{2.5})? If it is, could you provide a brief explanation why?

pp. 9-26, lines 28-31 & top of p. 9-27: If available, it would be informative to cite the coarse mass associated with the crustal and “metals” factors in Phoenix. Surely the “metals” (which may well be the causal factor here) represent a small fraction of the coarse mass (yet we’re about to embark on a new (and fairly useless) coarse mass measurement program).

9.2.2.2.4: This is not necessarily the place to address this unasked/unanswered question, but a detailed discussion of (short-term) lag periods clearly implies significant response from short-term exposures. The relevant question that might be posed somewhere is something like: Are health effects of PM most strongly associated with short-term exposures, long-term exposures, or both?

9.2.3.2.3: This lengthy, multi-caveat discussion feels like a re-summary of issues better addressed in preceding chapters (6 & 7). Too many “however’s”; too few simple declarative sentences.

9.2.3.2.5: Overall, a very informative discussion, clearly stated!

p. 9-62, line 20: By “fine fraction” do you mean “accumulation mode”, or everything less than 2.5? If its everything less than 2.5, it can’t have less surface area than ultrafines – which it includes. If its “accumulation mode”, it does not necessarily have a “much larger particle number” than ultrafines.

p. 9-63: This discussion of acid aerosols – which for the most part is nothing new – might benefit from a pointer to, or some additional discussion of the section 9.2.3.2.7 discussion of the influence of aerosol water – which is relatively new and informative. All things (RH) being equal, a more acidic aerosol will draw more water to aerosol phase than its neutralized counterpart and also further increase the solubility of some gasses, organics & metals (& decrease solubility of others).

9.2.3.2.7: Discussions of aerosol water and bio-aerosols seem new, helpful, and directly responsive to previous review comments.

9.3.1.1: I’ve previously commented extensively on visibility effects sections and won’t repeat – except to emphasize that differences between PM-2.5 mass and visibility effects are predominantly due to aerosol water – present in ambient aerosol and intentionally removed by the “artificially dried” regulatory, instrumental definition of “fine mass”.

p. 9-103, line 7: Add “artificially dried” before fine mass to make it clear you are not referring to the mass of fine particles in the ambient air – which has already been affected by the combination of relative humidity and the hygroscopic characteristics of the aerosol.

p. 9-104, lines 1-10: Since the last review, neither the algorithms & parameters used to calculate light extinction nor the measurement methods used to quantify visibility effects from aerosol species have changed for the (IMPROVE) program which is now the basis for calculating haze effects in class 1 federal areas. The cited Malm (2000) analysis showing improved performance

by considering sulfate ammoniation (at acidic GRSM) relates again primarily to a better estimate of ambient aerosol water content.

p. 9-104, line 15: add “rural” before “West”

p. 9-106, lines 1-4: could also add that these local standards have (at least in Denver) resulted in PM_{2.5} emissions & concentration reductions. Could also add that “similar threshold determinations, convergent on a minimal visual range of 40 to 50 km have also been identified in visibility standards in Lake Tahoe, the Fraser Valley and State of VT.” Two locations picking similar “adverse thresholds” is a coincidence; 5 is a convergence.

9.3.2: A substantial improvement over previous “ecological effects” discussions! But the question remains ambiguously avoided regarding whether eco-effects of PM include: PM deposited as (dry) PM only; PM (formerly present as PM in the ambient air) deposited by dry, wet & occult process; or PM & PM precursors deposited by various mechanisms. Much of the discussion relates to the latter (cumulative effects of PM and its precursors) definition, which seems important to include here – for later consideration of costs/benefits of attaining standards.

9.3.3: Not much content here, but pleased to see that EPA still (or again) considers climate change as potential environmental effect of anything...

9.3.4: Materials damage section is especially lame. Effects from PM & precursors are significant, but less considered here than 1996 CD or NAPAP SOST. Might be better to state clearly that “federal research funds have not been available to investigate the effects of PM and its precursors since the mid-1980s.”

Supplemental Comments on PM CD Chapters 8 and 9, R. Poirot 7/26/04

Several sections of chapters 8 & 9 (for example 8.2.2.5.3 & 9.2.3.2.1) summarize health effects associations with different chemical components and/or source categories on PM in various size fractions. These discussions are clear, detailed, helpful and informative – and (I think) the results could conceptually be presented, integrated, summarized, etc. in two general ways:

1. to indicate that many or most all of the major PM mass-contributing species or source contributions have been individually shown to be injurious (this adds considerably to the use of PM_{2.5} or PM_{10-2.5} mass as a regulatory metrics, regardless of different PM mixtures in different regions).
2. to indicate that some species or source categories appear to be more harmful or less harmful than others (potentially this might lead to species-specific standards or source-specific priorities in the implementation phase).

Based on discussions at the CASAC PM CD review, subsequent discussions at the PM coarse monitoring methods review and on a re-reading of relevant sections of chapters 8 and 9, I

encourage EPA to more heavily emphasize the former (#1) use of this information and de-emphasize the latter (#2). General reasons include:

- a. Adverse health effects are associated with many different species and/or source-specific contributions, although these associations are not always consistent among studies. Taken in the aggregate, they clearly show adverse effects from many species, but individually no one study is definitive.
- b. The species and/or source-specific health associations are not sufficiently strong or consistent in their findings to support species-specific standards or to prioritize (or exculpate) species or sources for future controls at the present time – and to do so would require choosing among or rating studies which show contrary effects (a much more difficult argument to support than #1).
- c. Epi. studies associating specific source categories with effects (or non-effects) are limited in number, and have generally have relied on “factor analysis” approaches (such as PCA with Varimax or Procrustean rotation) which are not currently considered state-of-the-science (poorly constrained and potentially yielding many different “equally correct” answers) and require subjective interpretation of the resulting sources. These results are then often further interpreted and commented on in the CD in a highly speculative manner.

Specifically, I think the chapter 9 integrated synthesis should de-emphasize or present counter examples in sections where specific source categories are identified as uniquely benign. This seems most evident for the contributions of “crustal” emissions to PM_{2.5}, PM₁₀ and/or PM_{10-2.5}. I think this is especially not helpful in considering any coarse particle standards, since crustal material (and its associated anthropogenic chemical or biological contaminants) is typically a large fraction of coarse mass at most times & places. For example following are several examples where I think the potential effects of “crustal particles” are unnecessarily (& speculatively) de-emphasized:

On p. 9-44, lines 18-19: “Also of much importance, all of the above studies that investigated multiple source categories found a soil or crustal source that was negatively associated with mortality”. Here, its not entirely clear why this is “of much importance” (compared to what?), or what “all of the above studies” refers to (the preceding paragraph, page, section?). The consistent finding of a negative association (and implication we would live longer if it were dustier) is a consistent indication (to me) of a poorly formulated model(s). It is also inconsistent with the many studies (mostly cited in the CD) which do show effects associated with coarse particle mass, and with the rather extensive bodies of literature on adverse effects from both the inorganic components of crustal material (silicosis, pneumoconiosis, etc.), as well as with the extensive and growing literature on diseases associated with soil-borne fungi or bacteria (Coccidioidomycosis, etc.). I’ve listed some references grouped in these 3 general areas at the end of these comments.

Several features of the (rather outdated) receptor model approach taken by the studies which I assume are referred to in “all of the above studies” are important. First, all multi-elemental

measurement techniques, and especially the most common XRF, coincidentally quantify a large number of elements which are of predominantly crustal origin (Si, Al, Fe, Ca, Ti, etc. – much more so than for any other source category). For this reason, a “crustal” or “soil” factor is nearly always identified in virtually all receptor model applications. The (rotated eigenvector) factor analysis approach which I think was used in all of the above studies seeks first to account for the collective variance of all the species used as input, and so typically (prior to rotation) the first component, explaining a maximum of the total variance tends to be “crustal” (even though these elements together typically account for only a small fraction of the fine mass). Subsequent rotational schemes (Varimax, Procrustes, etc.) then redistribute the variance in ways that require highly subjective decisions by the modelers. These models also require (can only find) sources of fixed, unique chemical composition and variable, unique contribution. Soil itself has a highly variable composition but tends to be more alkaline in the West than in the East, very alkaline in areas with calcareous bedrock, and different yet again in the Sahara Dust and Asian Dust which often result in the highest soil contributions in the Eastern US and West coasts respectively. These more distant dust events also tend to have much smaller particle size distributions than “local dust” emissions, as the larger particles are more readily removed during transport. Crustal material can become heavily contaminated with anthropogenic S, N, OC, EC, salt and metals – both as it is deposited & resuspended from roadways or as it undergoes chemical reactions during transport. Conversely, many other sources also contain “crustal impurities” (coal fly ash for example), and so when one obtains a “pure crustal source” from a factor analysis its not entirely clear what that source actually represents. If the rotation is oblique, the sources are required to be uncorrelated, and it’s therefore highly probable that the “crustal” source will (to the extent local sources contribute) be a good indicator of high wind speeds, since this will lead uniquely to high emissions & concentrations of dust which will be uncorrelated with all other (gaseous &) particulate pollutants. While high dust concentrations that also build up under stagnation conditions (from road dust emissions) or dust from more distant origins will tend to get mixed into other modeled sources. Quite possibly the consistent finding of negative health associations with dust just reflects windy days when folks stay indoors and the air is otherwise at its cleanest. For example:

On p. 9-27, lines 1&2, we learn that “new studies have shown no increases in mortality on days with high concentrations of wind-blown dust (crustal particles), using PM 10 concentrations and data on wind speed as indicators of dust storm days.” Which new studies? I think the (not unreasonable) use of wind speed as a dust surrogate is telling, as dust emissions (especially the maximum concentrations) are uniquely associated with high wind speeds – which in turn will tend to minimize concentrations of all other (fine) particle and gaseous components – assuring minimal chemical reactions between crustal particles and other species. High concentrations of crustal particles and chemically associated contaminants (on the surface of coarse particles) from MV, SO₂ or smelting activities would also reach high concentrations (as would many other gaseous and PM pollutants) on local stagnation days with low mixing heights – but would not be considered with this “wind speed” surrogate (nor would dust of distant origin). Potentially outdoor activities are curtailed on very windy, “local” dusty days, windows are closed, inhalation efficiency of coarse particles likely decreases with wind speed, and the spatial representativeness of “central site monitors” diminishes. Conversely, the lengthy Section 8.4.3.5 discussion of “Adjustments for Meteorological Variables” includes factors like temperature and humidity that

might tend to exaggerate assumed PM effects, but makes no mention of wind speed - which might tend to diminish such effects.

On p. 9-27, lines 3-6, it is postulated that cardiovascular mortality in Phoenix may be due to the metal rather than crustal content of coarse particles. Yet on p. 8-63, lines 22-28 it's indicated that "... (Smith et al., 2000) indicate that coarse particle-mortality associations are stronger in spring and summer, when the anthropogenic metal (Fe, Cu, Zn, and Pb) contribution to PM10-2.5 is lowest, as determined by factor analysis." In this case, the seasonal association of effects when crustal, not metal, coarse particles are greatest is attributed speculatively to "biogenic processes (e.g., wind-blown pollen fragments, fungal materials, endotoxins, and glucans) of the particles during spring and summer". It is also specifically emphasized that the authors "observed that the implication that crustal, rather than anthropogenic elements, for the observed relationship with mortality was counterintuitive." Thus a finding that does not fit the theory is discredited.

Emphasizing the potential importance of coarse biological content is reasonable, but on p. 8-326, lines 8-17, it's indicated that "Reasons for differences among findings on coarse-particle health effects reported for different cities are still poorly understood, but several of the locations where significant PM10-2.5 effects have been observed (e.g., Phoenix, Mexico City, Santiago) tend to be in drier climates and may have contributions to observed effects due to higher levels of organic particles from biogenic processes (e.g., endotoxins, fungi, etc.) during warm months."

Here, I can understand how dry climate can and does lead to increased emissions and concentrations of coarse crustal material (and any biological material it contains), but I'm not sure why or if it's logical to expect arid climates (and associated sparse vegetation) to have uniquely higher pollen, endotoxin or fungi emissions & concentrations than humid areas – where wind-blown dust emissions would tend to be suppressed by precipitation, and where pollens, pollen fragments and fungi might be relatively more abundant.

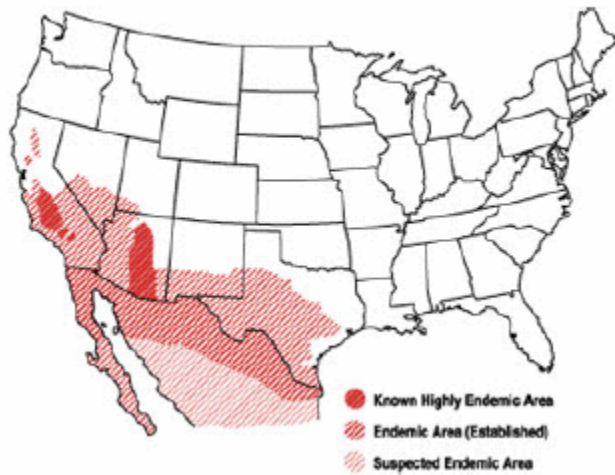
I think a more logical explanation could be effects from soil-associated fungi, which for the most part become airborne only as the soil becomes airborne during "natural" dust storms and/or as modified by human agricultural activities (tilling harvesting, grazing, etc.) and on & off-road vehicles.

For example, the geographically-focused incidence of "Valley Fever" specifically caused by the fungus *Coccidioides sp.*, which grows in soils in areas of low rainfall, high summer temperatures, moderate winter temperatures, and which is emitted in direct association with the soil that supports it, would seem like a more logical causal or contributing factor than some non-soil-related biogenic contribution from pollen or more benign fungi in general. See also the references on other soil-related fungal or bacteriological effects on human & animal health, crops, aquatic ecosystems, etc. – for example Garrison et al. (2003).

On p. 8-326, lines 17-21 it is indicated that "in some U.S. cities (especially in the NW and the SW) where PM10-2.5 tends to be a large fraction of PM10, measurements, coarse thoracic particles from woodburning are often an important source during at least some seasons. In such situations, the relationship between hospital admissions and PM10 may be an indicator of response to coarse thoracic particles from wood burning."

Spatial Distribution of Valley Fever

Source: <http://www.valleyfever.com/>



However, since wood smoke concentrations are VERY predominately $< 2.5 \mu\text{m}$, it seems illogical that wood smoke should be the likely causal factor for coarse particle effects in areas that have high coarse:fine ratios. I also question whether the NW has a high coarse:fine ratio and why the (dusty, crusty) SW would tend to have a uniquely high coarse wood smoke contribution (compared to all northern areas where space heating demands and fuel wood supplies are greater). This also seems inconsistent with the “counterintuitive” Phoenix results indicating highest coarse PM effects in the spring & summer. I’m getting picky here, but again it looks like trying too hard to show “it must be anything but crustal emissions”...

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Dr. Frank Speizer

Review of Chapter 7
Submitted by F.E. Speizer

Summary Comment:

Section 7.201

I found the summary (section 7.9) difficult to read. This is mainly because, although it professes to be interpretive on toxicologic findings, from pages 7.201 to the end of section 7.92.2, it is mostly a catalog of the findings in animals both positive and negative with little interpretation of the relevance to the human mechanisms of interest. The next section 7.9.2.3 on seems to have been written by a different voice in that the toxicologic findings are presented in a much more interpretive mode to explain, where possible, the human finding reported by the epidemiology. It just may be that the data are more clear for the last half of the summary than the first half, but I doubt it; particularly since most of the agents mentioned have been studies far less than those mentioned in the first half. Examples of sentences that are not helpful:

p. 7.206, lines 25-27

p. 7.206, lines 28-29

p. 7.207, lines 23-26

p. 7.208; lines 24-25 (what is good of studies negative in animals but positive in humans?)

This is also apparent in some of the tables. It seems that the authors are losing their focus. The purpose of the toxicology is only partly to understand the mechanism in animals, but surely to understand it when it is relevant to humans.

Side Issue:

I really doubt Gohio and Devlin (2001) statement that average ventilation of active person is 15 /min for 24 hours. If I give an active person 2 hours at 30 /min; 8 hours of sleep at 5 /min, and 14 hours of wake time at 10 /min (generous) that only comes to 10 /min for the 24 hours..

Review of Chapter 8
Submitted by F.E. Speizer

General Comment:

This is a much more readable draft than the previous one. The format of reviewing the 1996 document followed by the new material seems to work well. I think the chapter is ready to be signed off on with very minor modifications the staff should be able to handle. Most of the comments below are for editing and clarity. I found section 8.4 a particularly useful summary that for the most part reads like it belongs in chapter 9.

Specific Comments:

Page 8.11; Line 29

Change “eliminate to “control for”

Section 8.1 to page 8.17

Although this discussion is accurate in what it lays out and tries to do, it is still not clear to me that it belongs in a criteria document. It would be much more reasonable for a preamble to the staff paper in that it provides a framework for interpretation rather than a criteria for inclusion. Having been done, leave it in, but consider not including it in future C.D.’s.

Page 8.61; Summary paragraph, beginning Line 16

Perhaps one additional point should be added regarding size fraction, in that there appears to be a regional component to the apparent coarse fraction response, in that in western cities the $PM_{10-2.5}$, measured or indirectly calculated, appears more likely to be significantly associated with total and CVD mortality. This could be related to somewhat lower $PM_{2.5}$ levels as fractions of total in west vs. east.

Page 8.106 at Line 11

Need to provide a brief summary statement on AHSMOG study.

Page 8.114

Where comparisons are made among studies, suggest add one on VA sites that match ACS sites. Still not clear what pollution averages were used in VA and how adjustment for “background” modifies these averages.

Page 8.116; after Line 4

Add issue of selectivity of the cohort as being at greater risk of hypertensive disease and, as indicated by Lipfert, possibly depletion of at risk subjects.

Remarkable consistency of results seen for cohort studies. The difference seen in the later Lipfert studies for $PM_{2.5}$ is really the only inconsistency and may relate to competing risk in an aging population; e.g., as risk goes up in older population, may be harder to see effects of pollutant. Opposite to the increasing relative effect of smoking as risk of dying in ex-smokers/non-smokers goes down, relative risk of smoking goes up.

Chronic cohort studies summarized well and give consistent result for $PM_{2.5}$. The results for $PM_{10-2.5}$ much more tentative and inconsistent.

No effects of $PM_{10-2.5}$ on CVD morbidity or ER visits.

Page 8.146; Line 18

Change to be specific to indicate that there was a significant association with $PM_{10-2.5}$ for Ischemic heart disease, but not for dysrhythmias or heart failure.

Page 8.151; Line 26-27

Statement not true. There appears to be a clear and consistent finding that PM_{10} and $PM_{2.5}$ are both associated with acute CVD effects. What is not clear is the effect of $PM_{10-2.5}$, which is inconsistent.

Page 8.161; Line 1-6

This represents too negative a statement for the results seen. It is true that the results across studies are different, but what is consistent is that there are changes in electrophysiologic parameters that

are associated with PM. They may be different in different studies, but that should not negate their importance and therefore it is inappropriate to say that no conclusion is possible.

Page 8.165; Section beginning with Line 5

Need to specify consistent PM₁₀ and PM_{2.5} results. No consistent results for PM_{10-2.5}.

Page 8.165.

Add section on electrophysiology. Results are significant, but because the interpretation are not yet understood, doesn't mean the effects should be ignored. The effects are just as interesting as are the blood characteristic effects (see line 13.)

Page 8.189; Line 25

Add sentence: "However, there were consistent significant decrements in PEFR for those regions where the mean levels of PM₁₀ exposures were 47 /m³ or higher."

Page 8.193; Line 10

Add: Again for those communities with higher average levels of PM₁₀ exposure the results were consistent.

Section 8.4

Is a well-organized interpretive summary of the entire chapter. It reads quite well and potential with other summary components might become a major section of Chapter 9. Having not seen Chapter 9 yet, I am not sure that one will not be redundant for the other, at least as far as the epidemiology is concerned.

Chapter 9 Integrative Synthesis

Review submitted by F. Speizer

General Comments: The chapter is organized in a much better way than previously. However, the last part of chapter 8 appeared to be a much more readable section that integrated and summarized much of the material. I would have liked to have seen much of that more directly incorporated. Here, we seem to have several writers who have taken different approaches to summarize the data. In some cases we get brief summaries without references, in others we get detail with specific references or specific references to earlier chapter segments. What this does is to emphasize some findings and de-emphasize others. A single science editor needs to go through (and shorten) the whole chapter. The content seems appropriately reviewed and the overall emphasis seems right. Therefore staff may be able to move forward to closure, given the input without further CASAC review.

Specific Comments:

Page 9.19, line 2: Typo "known"

Page 9.23, line 14: Should this first line PM_{2.5} be PM_{10-2.5}?

Page 9.24, line 5: this should be Figure 9.6.

At the end of this section it seems to me that a comment is warranted that for both mortality and morbidity the effects of PM10-2.5, although not always significant was generally larger in magnitude for respiratory effects vs. cardiovascular effects.

Page 9.28, line 1-2: More detail is needed here on the VA study. It is my understanding that the analyses done in the earlier years showed a significant or at least consistently positive result and it is only the later years when potentially susceptible subjects had been lost that no effect was seen.

Section 9.2.2.2.5, page 9.37-38: This is an interesting argument. A convincing story is given for making any estimate of a population threshold almost impossible to interpret, and then the discussion proceeds to try (unsuccessfully) to get beyond linear. Not sure this makes sense. Why not simply leave it at a population threshold is irrelevant?

Page 9.39, line 21: Change to read: “... morbidity effects, particularly as related to respiratory diseases. Little evidence.”

Page 9.45, lines 3-12: this is an indication of serious editing needed in this Chapter. This entire paragraph is a repeat in content of what is said earlier in the chapter.

Pages 9.45-9.54. All section labeled under 9.2.3.2.2-...3: This section seems far too long and detailed for an “interpretive synthesis”.

Page 9.56, last sentence beginning on line 6. It seems to me that the toxicology is not being done to find a **causal relationship**. The purpose is to understand mechanisms that explain the associations that have been found. The tone needs to be changed to reflect this.

Page 9.67, para starting line 11: This paragraph on CAPS, in contrast to those around it contains only a generic discussion of CAPS rather than specific citations of findings as is done for the methods discussed in both preceding and following paragraphs. This is an example of the lack of consistent editing in putting together the chapter. Why cite specific experiments for one and not the other unless a value judgment is being made? If so then should be specified. If not a consistent approach is required.

Section 9.2.3.2.6 Mechanisms of action

This section is far too important to be limited to the space and detail presented, particularly in contrast to the discussion before on both the aerometrics and the toxicology. This minimizes the importance of what the basic issue is.

Page 9.85, line 2. At end of sentence should add: “primarily because specific studies with particles of this size simply have not been performed.”

Page 9.95, par 9.2.4.3. In this paragraph there are a number of places when extremes are suggested that really are not justified. Line 5, “most” important factors ...; line 10, potentially “great” importance. I think these need to be toned down (not eliminated).

Page 9.98, Table 9.6. May I ask that the authors check again on the source for this table. I am concerned that the last two columns may be reversed in that I would have anticipated for all of these conditions, not just acute bronchitis and pneumonia, that ages 65 + would have had higher rates than 45-64 unless this represents a reporting bias.

Dr. Barbara Zielinska

Review of revised Chapters 7, 8 and 9 of PM Criteria Document

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Comments on revised Chapter 9, “Integrative Summary”

In my opinion, this chapter represents a significant improvement in comparison with the previous version. However, I have some concerns, which are detailed below:

1. This chapter is still too long and not uniform. Some sections truly present the synthesis of the information from previous chapters, whereas some other sections repeat the results of the individual studies. Some sections give the references to the individual studies, some not. I suggest referencing those papers only that were not referenced in the previous chapters (this would greatly reduce 22 pages of references). I think that a consisted editing of Chapter 9 would be very useful.
2. The Chapter is lacking a summary concerning the ambient trends in PM_{10} and $PM_{2.5}$ (when available) concentrations since the last 1996 review (i.e. some summary of Chapter 3). Also, a short summary concerning the changes in chemical composition of PM over the years would be appropriate. In my opinion, this is important information that would put the exposure data into a proper context.
3. Section 9.2.3.2.8 concerning the coherence of evidences, discusses the Utah Valley study in great details. Although this study is certainly very valuable in showing the relation between health effects and emissions from a very specific source, i.e. a steel mill, it does not necessary relate to the general ambient PM in the U.S. As I pointed out in my previous reviews, the fact that the hospital admission was greatly reduced after the steel mill closure, indicates that not all ambient PM is created equal and that the PM health effect depends greatly on its sources and chemical compositions, not only mass concentration. So, it is not necessary “coherent” with the results of epidemiological studies.
4. In addition, as I pointed out before, the Utah Valley instillation study used the extracts from the 10 years old PM_{10} filters. The filters were stored in plastic sleeves at room temperature and humidity and they might be subjected to significant artifacts over the years of storage in these inappropriate conditions.
5. Although Section 9.2.3.2.7 that discusses the inhaled particles as potential carriers of toxic agents is very interesting, it doesn't really belong to this Chapter, but rather to Chapter 7. Only a short summary should be included in Chapter 9.
6. Minor comments:
 - Is Appendix A necessary?
 - Page 9-23, line 14: This should be $PM_{10-2.5}$ rather than $PM_{2.5}$.
 - Page 9-30, line 30-31 and page 9-31, line 1-2. The statement that gaseous co-pollutants act as surrogate of PM is highly speculative

- Page 9-65 says that the organic constituents remain of concern regarding PM health effect due in large part to the contribution of diesel exhaust particles to the fine PM fraction. However, the organic compounds emitted from other combustion sources, such as gasoline vehicles, are not very different... In addition, little is known about the atmospheric transformation products of different emissions. One would argue that organics remain of concern because some of them are known air toxics, regardless of the source.

On a positive note, I found the discussion regarding caveats and limitations in interpretation of human and laboratory animal PM exposure data in Section 9.2.3.2.2 (approaches to experimental evaluation of PM health effect) very valuable. However, this seems to be a stand-alone section, and its conclusions are not reflected in any of the subsequent discussion. On the contrary, the Chapter uses excessively such adjectives as “considerable”, “strong”, “extensive”, etc., when presenting the evidences of PM health effects.

Comments on revised Chapter 7, “Toxicology of Particulate Matter in Humans and Laboratory Animals”

In general, I found this chapter significantly improved in comparison with the previous version. I have a few minor comments:

1. Although some limitations of CAPs exposures described in this Chapter (such as ineffective concentrations of particles smaller than 0.1 microns in diameter and elimination of gases by the concentrators used at that time) are pointed out on page 7-24, these limitations are not reflected in the Summary section.
2. Section 7.2.1.2, page 47-49 discusses the Utah Valley study; see my comments No. 3 and 4 above.
3. Page 7-78, line 19: term HULIS includes not only bioaerosol, but also most probably some combustion generated and secondary organic compounds.
4. Page 7-159: Section 7.2.1.4 is really 7.7.1.4
5. Page 7-180, lines 1-8. It should be benzo[a]pyrene, not benzo[z]pyrene. Polycyclic aromatic compounds (PAC) are ubiquitous in the environment and their sources include not only noncatalyst-equipped gasoline vehicles (not very common today or even in 1993 when the ambient samples were collected) but also catalyst equipped gasoline vehicles (especially older and higher PM emitters), diesel vehicles, natural gas combustion, and other combustion sources. 2-Nitrofluoranthene is the secondary product of atmospheric reactions worldwide (see, for example, Ramdahl et al., 1986) not only in the Los Angeles area.
6. Page 7-181, line 22: benzo[a]pyrene, not benzo-a-pyrene
7. Page 7-182: what are highway-emitted PAH-like compounds?
8. Page 7-197, line 16-18: decreased mutagenicity suggested nitroarenes? This doesn't make sense.
9. Page 7-198, line 25-26: organic fraction is more mutagenic than the PM component? Which PM component? Isn't organic fraction a part of PM?
10. Page 7-199, line 12: ethylene
11. Page 7-210, line 32 and 7- 211, line 1: again, strange statement: organic fraction appears to be more mutagenic than the PM component (see 9 above)

12. Page 7-212, line 1-3: It is difficult to rank mutagenicity according to the fuel type; rather, the efficiency of combustion processes may play more important role.

References:

Ramdahl, T., B. Zielinska, J. Arey, R. Atkinson, A.M. Winer and J.N. Pitts, Jr. (1986). Ubiquitous Occurrence of 2-Nitrofluoranthene and 2-Nitropyrene in Air. *Nature*, **321**, 425-427.

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

The revised Chapter 8 represents a significant improvement in comparison with previous versions. I'm not an expert in epidemiology, but I found Section 8.4 and 8.5 readable and very useful. In my opinion, this chapter is ready to be accepted as final with some minor revisions. I have only a few comments:

1. The paper by Hoek et al. (2002), if left in the final version in Section 8.2.3.3.3 (p. 8-124 - 125), should be appropriately qualified. NO₂ is not a good tracer of motor vehicle emissions; in fact it is mostly a photochemical reaction product of NO, which is emitted by motor vehicles (primarily diesel vehicles). There are also other sources of NO_x (for example, power plants) and the assumption that 50% of NO₂ is coming from motor vehicles may or may not be correct, depending on the specific area. In addition, the exposure data in this paper were estimated, not measured.
2. The statement that Coefficient of Haze (CoH) is a good PM index for motor vehicle sources (Section 8.2.2.5.2, p. 8-66) is odd. CoH is not a PM component (p.8-66, line 25-26), but it is related to the amount of fine PM in the atmosphere. It reflects the contribution of all sources, not only motor vehicles.
3. Page 8-72, line 12. Pb is no longer a motor vehicle tracer in the U.S., since unleaded gasoline has been used since over 20 years.

Dr. Jane Q. Koenig

Comments of Ch 9
Jane Koenig
July 10, 2004

In my judgment the Integrative Synthesis is well written. However I continue to believe, strongly, that these documents should be much more concise than they are. I don't see the need to repeat data in this chapter. Supposedly the description of the data was accomplished in earlier chapters. Just as a matter of interest, and to reinforce my point, I refer EPA to a recent American Heart Association Scientific Statement on associations between heart disease and air pollution (Brook et al. *Circulation* 2004; 2109: 2655-2571. In 17 journal pages, there is an excellent description of the deleterious effects of ambient air pollution on health and its relation to heart disease and stroke. I believe that journal review would convince most people of the association between PM and cardiovascular disease.

Page 9.5 Should there be some mention of the fact that some individuals voted for a PM1.0 indicator?

9-10 Table 9-1 is a good addition as is Figure 9-3.

9-18 I don't know if the quote from the 1996 CD makes the point desired. It seems a true statement today.

9-35 Selection of lag certainly can obscure associations. But what is the alternative?

9-38 The findings from intervention studies may make the strongest case for a more stringent standard.

9-39 to 9-71. This seems to be mainly a rehash of text from Ch 8. (and 7)

9-72. The format seems to change at this point. What is the significance of the Bold heading?

9-80. introducing the concept of coherence is good. Might use some sort of pyramid of effects from changes in pulmonary function to inflammation -to hospitalization- to death?

9-85 In the second full paragraph the authors compare exposures to doses. This text should be cleaned up.

9-95. Attempts have been made to rate the public health impacts of air pollution. Eg. Report of an expert panel to review the socio-economic models and related components supporting the development of Canada-wide standards for PM and Ozone (*J toxicol Environ health*, 2004; 7 (3).

This section brings up the association between PM and lung cancer and also between PM and diseases of infancy but doesn't seem to work these data into the general conclusions.

One section that may be lacking, is a description of short term effects based on PM metrics of less than 24 hours. These data are needed for consideration of a short term averaging time for PM_{2.5}.

In general with a little editing I judge Ch 9 to be sufficient for its purpose and recommend that we not attempt to make it reflect individual tastes but keep an eye on the big picture. Does this chapter adequately reflect the material presented in the CD and does it give EPA an adequate synthesis for writing the staff paper? I think it does.

I have no additional comments on Chapters 7 and 8 beyond what I said in the past.

Dr. Petros Koutrakis

Chapter 7

Page: 7-4, Line 8: The reproducibility of particle composition from day to day may be a problem; however, one could take advantage of this and investigate associations between health effects and composition. The Godleski CAPs studies have been very successful in doing this.

Page: 7-4, Line 10: To date there are coarse and ultrafine concentrators which can make it possible to expose subjects to coarse and ultrafine CAPs.

Page: 7-6, Line 2: We are now conducting a study where we investigate the toxicity of primary and secondary particles from coal power plants, the TERESA study. The toxicity of primary particles may differ from that of secondary particles due to the photochemical reactions that can result in many reactive compounds.

Page: 7-50, Line 15: I am not sure that there are many atmospheric studies that have examined the relative concentrations of water soluble and non soluble metals in PM. If such a strong statement is made then it is necessary to back it up with some data. My guess is that PM metals are mostly in the form of sulfates and nitrates and are quite soluble.

Page: 7-148, Line 14: Godleski and his group used a similar exposure scenario for MI rats. CAPs were found to reduce HRV. Ozone was not found to have a synergistic effect. The experiment needs to be replicated before publication.

Page: 7-155, Line 18: Mass is not the only important parameter. Composition may also play an important role.

Page: 7-204, Line 16: Include reference

Page: 7-204, Line 20: Include reference

Chapter 8

Page 8-1, Line 5: I congratulate the authors for their hard work. I am sure that it was quite difficult considering the plethora of information that was reviewed. Although the text was very long, it was nicely structured so it was relatively easy and enjoyable to read.

I have made many individual comments but my two major ones are the following:

1) Although I think we need to set up a coarse particle standard, I am not sure that the available information is sufficient or convincing. One can argue that for the previous PM standards we did not have enough information and that the decision was based on our scientific judgment. For example for the fine particle standard we had only a handful of papers but it made sense to

prepare a new standard and we did so. In the case of coarse particles we do have some information but is not coherent. I hope that it will be kept in mind when final recommendations are made about the levels of the new standard.

2) My second major comment is about the interpretation approach. In the beginning the chapter claims that no calls will be made about which methodology is right or wrong and I absolutely agree with this. As the authors suggested, the conclusions will be based on the collective available information. However, I found that the rule was not followed consistently. For instance, some individual papers received too much attention in spite of what relatively little they had to say, while the chapter did not try hard to synthesize information from large studies. However, this was not done intentionally to prove a particular point.

Below please find my individual comments:

Page 8-13, Line 12: This is an important point and represents the cornerstone of the epidemiology chapter. I agree that this is the only way one can approach such a complex issue. However, the evaluation process could become subjective and one should be cautious.

Page 8-19, Line 15: I assume that the CD refers to exposure error. If this is the case I suggest calling it as such or exposure misclassification.

Page 8-19, Line 16: “Functional” refers to dose-response relationship?

Page 8-19, Line 19: Of course, a major criticism of the epidemiological studies during this time was the biological plausibility. One remembers that very little toxicological information was available.

Page 8- 49, Line 7: It is apparent from both the multi-city and single-city studies that risk factors are higher for the Northeast. This is quite an interesting finding and is in agreement with the Boston and New York CAPs studies.

Page: 8- 54, Line 2: Attributing effects to the difference of sampler sharpness is pushing it and is scary!

Page: 8- 54, Line 26: Measurement error is so vague. Can you please specify?

Page: 8-57, Line 1: Although I believe that we need a coarse particle standard, I think that cited literature on coarse particle health effects is not compelling at all. If Table 8-2 represents the state of knowledge about coarse particles then we’ve got a problem.

Page: 8-61, Line 28: Most of the lower risk estimates are not statistically significant.

Page: 8-63, Line 17: This statement was made before and I had commented on it. The way it is presented here is confusing. It is not clear that it is the Mar analysis and not the Laden.

Page: 8-66, Line 11: The literature for ultrafines is extremely thin and this is reflected by the above discussion which concerns one group and one study.

Page: 8-116, Line 12: From the acute studies one can see that Northeastern and Midwestern studies show higher PM relative risks. Therefore, the higher risks found by the Harvard Six Cities study are in agreement with the acute studies, since the six cities are located in the Midwest and Northeast.

Page: 8-128, Line 2: It is unrealistic to compare Dublin, APHEA, and Utah while expecting to make perfect sense. We talk about different populations, climates and, more importantly, composition. So it is silly to draw important conclusions about acute and chronic effects.

Page: 8-128, Line 21: Is life expectancy per year the correct term? If so, then the effect is unbelievably huge.

Page: 8-129, Line 7: Maybe there are no effects associated with sulfur dioxide. Note that the other pollutants stayed more or less the same.

Page: 8-130, Line 3: I think we have sufficient findings which guide us towards the importance of acute effects on mortality. Putting together the results from the intervention studies, where immediate benefits can be seen, one should start to think that acute effects/exposures are substantially more important than the chronic ones. Furthermore, I was impressed by the second follow-up of the Six Cities (not published yet) where concentration decrease in Steubenville meant decrease in mortality risk. In fact when both the first and second follow-up data were put together, Steubenville 1 and 2 looked like two different cities. Actually, the whole analysis looked like a twelve city study. The time between the two follow-ups was about 10 years so one can conclude that the population managed to recover in that time span. Some other preliminary analysis by our EPA Center suggests that for chronic effects only the last year of exposure matters! I am really starting to believe that maybe there are no chronic effects! We become susceptible because of age, genetics, food, smoking, income, and maybe air pollution but a daily event can kill us. It may sound heretical at this point but the little evidence tells us that we should start exploring this hypothesis.

Page: 8-131, Line 26: We need to mention that Six Cities and ACS cover different geographic areas.

Page: 8-165, Line 5: How about the Six Cities/Factor analysis by Laden et al?

Page: 8-297, Line 10: Central site monitoring data may be inadequate to assess population exposures to coarse particles due to the high spatial variability of coarse particles. Also coarse mass measurement error is higher than that for fine particle mass. Therefore investigation of the short-term effects of coarse particles and comparing them to those of fine particles is not a trivial task.

Page: 8-315, Line 6: Variability of concentrations may also be an important factor. As bigger day-to-day variations may result in a stronger health effects signal.

Page: 8-322, Line 22: I am surprised that this is all we get in this important issue. In the future we need some more thinking in this area because this is the million-dollar question we all want to answer.

Page: 8-326, Line 2: I do not think that the information provided about ultrafines supports this statement.

Page: 8-326, Line 5: The evidence provided by this chapter was so inconsistent, Therefore the statement "may contribute under some circumstances" is not substantiated.

Page: 8-326, Line 17: Road dust is an important type of coarse particle that may be of health interest.

Chapter 9

Page: 9-1, Line 2: Overall the authors did a nice job. I have two main points:

1) The synthesis chapter should be shorter. One hundred plus pages is too long and defeats the purpose of this chapter. It is not necessary to include summaries of the different chapters, which was done in some cases. One should present the distillation of ideas outlined by the different chapters. It is a difficult job but can be done.

2) In some cases I found that the synthesis chapter included information (or put emphasis) on things which were not discussed (or stressed) in individual chapters. One example is the hypothesis about radicals and peroxides. This is a hypothesis and nothing more and should not be in the synthesis chapter.

My specific comments follow below:

Page: 9-1, Line 12: This is a good point.

Page: 9-6, Line 4: The physico-chemical properties of coarse and fine particles are very different. On this basis it makes sense to develop separate standards for these particle types. However, one should not ignore the fact that epidemiological and toxicological information regarding coarse particles is very limited. Similarly, very little is known about human exposures to coarse particles. The situation was similar when the PM10 and PM2.5 standards were proposed and I am not, therefore, overly concerned. However, I am concerned about the heterogeneity of coarse particles both in terms of their origin and composition. Controlling road dust and desert dust is not the same. This is an important issue that has not been addressed by the CD. Maybe chapter 9 will deal with this somehow.

Page: 9-13, Line 6: This is a good discussion about PM exposure. It is somewhat speculative due to the lack of real data, but the statements made are sound. One important issue that was omitted is the inter-home and inter-city variability of the PM penetration efficiencies. Studies

have found that homes behave differently and thus the same outdoor concentration may reflect different exposures. An important factor affecting indoor/outdoor ratios is home ventilation that depends on house characteristics, city, season, etc. This issue is not important for acute studies but it can be for chronic ones.

Page: 9-18, Line 2: Does this include the re-analyses/confirmation of some studies: e.g. Harvard Six Cities and GAMs?

Page: 9-25, Line 7: This is not clear to me.

Page: 9-27, Line 5: Too speculative to be included in this Chapter.

Page: 9-27, Line 12: I would say that there is no evidence for the ultrafine story.

Page: 9-31, Line 21: Nowadays, where SO₂ power plant emissions are lower, SO₂ may also be tracer of diesel emissions. This is a thought!

Page: 9-37, Line 12: I found the lag section superb.

Page: 9-42, Line 23: Not enough information to understand Table 9-3.

Page: 9-43, Line 1: Meteorology also adds collinearity between species concentrations which makes source separation very challenging.

Page: 9-45, Line 12: This section should conclude that the information about toxic components/sources is non-existent. There are a couple of papers only and this is not enough.

Page: 9-47, Line 8: This is wrong! The majority of CAPs studies have done extensive characterizations of the particle exposures.

Page: 9-47, Line 19: Who wrote this?! There are ultrafine and coarse particle concentrators! Gases can be added as desired to the exposures. I strongly disagree with the philosophy of the CAPs section and strongly suggest that it be changed. More importantly it does not reflect the opinions written in the preceding chapters.

Page: 9-48, Line 9: Again ROFA has its pluses and minuses but being completely negative is not acceptable. Again this does not reflect the spirit of the rest of the CD. Furthermore, this is the synthesis chapter and one would like to know if one has learned something from, for example, the ROFA studies.

Page: 9-48, Line 23: Again, similar points as for CAPs and ROFA. This section came from nowhere. It does not belong here.

Page: 9-53, Line 1: As I mentioned above, I think the CAPs studies are meaningless. The same comment applies to ROFA. We need to realize that there is no perfect approach, but we learn little by little from each of them.

Page: 9-62, Line 9: This is not a recent study. In addition, many other epidemiological attempts to implicate ultrafine particles by the same authors and others have failed.

Page: 9-67, Line 17: There are several papers by Clark et al, Batalha et al, Saldiva et al which have shown associations between health outcomes and specific particle components, therefore this statement is not correct.

Batalha, J. R. F., Saldiva, P. H. N., Clarke, R. W., Coull, B. A., Stearns, R. C., Lawrence, J., Krishna Murthy, G. G., Koutrakis, P., Godleski, J. Concentrated Ambient Air Particles Induce Vasoconstriction of Small Pulmonary Arteries in Rats, Environmental Health Perspectives, 110(12): 1191-1197.

Saldiva, H. N., Clarke, Coull, B., R. W., Stearns, R., Lawrence, J., Krishna Murthy, G. G., Diaz, E., Koutrakis, P., Suh, H., Tsuda, A., Godleski, J. G. Lung Inflammation Induced by Concentrated Ambient Air Particles is Related to Particle Composition. Journal of Respiratory and Critical Care Medicine, 165:1610-1617, 2002.

Clarke, R.W., Catalano, P.J., Koutrakis, P., Murthy, G.G. Krishna, Sioutas, C., Paulauskis, J., Coull, B., Ferguson, S., Godleski, J.J. Urban Air Particulate Inhalation Alters Pulmonary Function and Induces Pulmonary Inflammation in a Rodent Model of Chronic Bronchitis. Inhalation Toxicology, 11(8):637-656, 1999.

Page: 9-67, Line 23: (See comment above)

Dr. Allan Legge

July 18, 2004

TO: Phil Hopke/ Fred Butterfield
FROM: Allan H. Legge

Review Comments: Section 9.3.2 Effects of Ambient PM on Vegetation and Ecosystems from Revised Chapter 9, Integrative Synthesis, Fourth External Review Draft, 'Air Quality Criteria for Particulate Matter, June, 2004'.

Overall Comment:

The authors are to be commended for concisely bringing together the key scientific information/understanding on vegetation and ecosystems from Chapter 4 as well as identifying the important data gaps and uncertainties which currently prevent relating ambient concentrations of PM to ecosystem response. The discussion of the potential application of the 'critical loads concept' in the U.S. opens a very important philosophical/scientific door for environmental protection in the future.

Other than a few minor comments, this section is acceptable.

Specific Comments:

1. Page 9-108.

i) lines 7-9.

It is important to note that sulfur is also closely linked with nitrogen.

ii) lines 11-13.

It should be noted that plants can also gain nitrogen nutrition from the atmosphere by taking up NO and/or NO₂.

2. Page 9-110, lines 6-7.

Point (4) as written is too restrictive. If the authors are referring to HNO₃, it can be formed without the presence of sulfur compounds.

3. Page 9-110, lines 12-14.

As phrased, this sentence seems 'overstated'. The intent of the authors is unclear. Later sections of the text, for example, show that Nr can be removed from a terrestrial ecosystem by NO₃- leaching. One can reduce Nr accumulation by reducing the emissions of Nr sources.

4. Page 9-114, line 1.

Suspect this should read "Acidic deposition and acidification of soils can lead to high Al-to-base cation ratios that limit"

5. Page 9-115, lines 14-15.

What is the intent of saying "- , rather than on those in sensitive ecosystems." Do the authors mean to say "- , rather than on rural exposures."

Dr. Paul J. Lioy

Chapter 9: Integrative Synthesis in the Air Quality Criteria Document for Particulate Matter – Draft #4

Comments of Dr. Paul J. Lioy Professor and Deputy Director of the Environmental and Occupational Health Sciences Institute, UMDNJ- Robert Wood Johnson Medical School

General:

The EPA has made a good faith attempt to provide an integrative synthesis of the results presented in the Criteria Document for Particulate Matter and should be commended for their efforts. I do have specific major concerns, but I believe that the Agency is on the right track for completing Chapter 9.

Chapter 9 presents concise summaries of the major findings found in the 1996 document; however, I do not always find a synthesis or contrast with recent results. There is an exposition of many findings, but there is not always a clear message as to how these have improved our understanding and filled gaps, or can be used to put to rest specific issues.

The results from Utah studies are extremely valuable, especially in terms of describing source to exposure to response relationships. They do not, however, represent the general or overall PM_{2.5} exposure - response relationships seen around the country. Thus, I do not think the results demonstrate “coherence” with respect to the general composition PM and health response. The results from Utah do provide very valuable insights into source specific pollution situations, and how reductions in a complex gas and particle mixture emitted by a particular source type can improve the health of a local population. *A very important scientific conclusion, and an important exposition within the context of accountability.* Thus, from the vantage point of a chapter on “integrative synthesis,” the results provide a very useful *case study*. It can be developed as a concise stand alone subsection that uses the available data on health outcomes, toxicology, ambient air quality and exposure, and source reductions

In contrast, the results from reanalysis of the Six Cities study on the reduction of health effects over time are compelling and must be considered (pg. 9-36) as part of the analysis for national PM_{2.5} and other air pollutant issues. They show that the character of the air has changed over entire cities. However, the questions that require discussion are: What sources have been eliminated or controlled.? What pollutants have seen significant reductions, and led to reductions in health effects.? Important questions requiring some analysis in a chapter on integrative synthesis. To summarize, a concise analysis of the above can tell us something about the sources which have contributed to PM and other pollutant related health effects. Further, the analyses may provide insights on ambient pollution exposure characterization needed for prospective health evaluations among US cities.

I am still a bit troubled by the discussion on toxic element linkage to PM health effects. The toxicological results for metals related health outcomes are for exposures that are orders of

magnitude higher than those found in the ambient atmosphere. Such a dichotomy does not provide much information for achieving “coherence.”

One issue that was given brief mention in the Chapter, has broad implications: *the timing of PM exposure with acute cardiac related health effects*. This appears to be a major scientific finding that has been made since the publication of the 1996 CD and the results strongly suggest that we may need to re-assess the form of the standard, and consider an acute PM_{2.5} health standard that is 2 to 8 hr in duration. This can be in addition to the 24 hr standard for short term effects. The issue may need a separate section. Promulgation of an acute health standard may not be feasible at this time, but the results indicate that more attention must be given to this issue in the future. I hope the Staff Paper that results from a *review of the final version of the CD* can at least provide discussion on an acute exposure standard

Conversely, the GAM issue did in fact appear to lower the exposure – response estimates for the chronic effects. What is the implication, if any, in terms of exposure response relationships used in the 1996 standard setting process? Would it change the conclusions about risk? I do not think stating that there is still a relationship is sufficient.

The chapter on air quality is almost ignored in Chapter 9. How has PM₁₀ and, where comparative data exists, PM_{2.5} changed since the publication of the 1996 Criteria Document. In its current form, the reader is left with the impression that we have major exacerbations of the PM standards. That is just not true. I think the issue needs to be correctly defined and characterized for the reader. The text discusses the % increase in risk/ 25 or 50 ug/m³ increase in PM_{2.5} and PM₁₀, respectively, but these values need to be placed into a context of the current situation. At the same time, the integration and synthesis should point out that controlling PM and other pollutants is reducing relative risks and these efforts need to be sustained in order to deal with current PM health issues, e.g. cardiac related health outcomes. This gap in the analysis of information provided in the CD can be filled using information from the chapters on air quality, *and should be added as a separate section on page 9.13 (Short but to the point), and appropriate revisions made to the conclusions on page 9.16*. As I reviewed the outline for this chapter, the requested changes fit well within the stated goals for Chapter 9.

Major Specific comments:

Page 9.3 lines 1 through 3. These numbered bullets do not make much sense. Please shorten the length and strengthen the points.

Page 9.3 lines 4-5, what do you mean by a coherent synthesis? A confusing statement.

Section 9.2.2 Some effort needs to be made to differentiate short term and long term health effects with respect to the timing of the onset of an event. A statement on page 9-36 suggests that we may need to start thinking about three standards acute – less than 24h, short term – 24 hours, and long term – annual. In a synthesis such information needs to be fully discussed to continue the quest “coherence “ within the chapter. I am a bit puzzled by the fact that that summary and conclusions for this section are so short and focus almost exclusively on the size

fractions when the results presented in the section discuss lags, and long term and short term effects. Overall, the section can use editing to reduce its size by about 25%

Figures 9.5 and 9.6 are excellent.

Section 9.2.3 *This section is much too long. It can easily be reduced in size by 60% and still convey the message.*

Page 9.45 Again there are statements about acute effects lines 4 to 12 which need to be folded into a synthesized discussion about the need to consider a shorter term, acute, standard.

Page 9-48 and others. I think that the conclusions need to make the point that metals exposures in toxicological studies are at much higher levels than ever seen in the ambient environment. I do not think that this message has been clearly articulated on page 9-84 or 9-85

Please eliminate the appendix. This information has been thoroughly discussed in chapter 8. You can reference chapter 8 for the interested reader.

Dated: July 14, 2004

Dr. Morton Lippmann

REVIEW COMMENTS

Chapter 7 of PM CD, Draft 5

M. Lippmann

General Comments

Chapter 7 is greatly improved for the fourth external review draft, and now represents a thorough and well-balanced review and analysis of a large, complex, and less than definitive literature on the associations between laboratory-based PM exposures and biological responses in humans, laboratory animals, and *in vitro* preparations. It could certainly be somewhat condensed to eliminate repetitious text, but that is not a serious failing at this point. As it stands, it can serve well as comprehensive and unbiased compendium and resource for Chapter 9 (Integrative Synthesis) and the OAQPS Staff Paper.

It now provides a more thoughtful and appropriate view, than did the prior drafts, of the nature and significance of the literature on: the short-term CAPs inhalation exposures; exposures to motor vehicle exhausts and extracts thereof; PM of biological origins; and interspecies differences in PM dosimetry. Also, it provides a more thorough and thoughtful discussion on the evidence supporting the plausibility of the epidemiology that points to cardiovascular causes of excess mortality and morbidity, and to excess lung cancer.

In my view, Chapter 7 now warrants CASAC endorsement and closure.

Specific Comments

<u>Page</u>	<u>Line(s)</u>	<u>Comment</u>
7-35	14-23	This discussion of a human exposure study seems to be out-of-place in this section.
7-117	10	What is a “vaporous milieu”?

7-150	17	The concentrations of NH ₄ HSO ₄ and O ₃ should be specified.
7-166	15	change “tissue” to “region”. The use of tissue implies that there is a uniform distribution of particles, which is far from the actual case.
7-192	20	Should a study published in 2004 be cited?
7-203	5	change “co-primary” to “the primary”.
7-211	22	change “mutating” to “mutations”.
7-198	26	What is meant by “the organic fraction being more mutagenic than the PM component”? Is it organic in the PM or VOCs?

Appendix 7A of PM CD, Draft 5

General Comments

This revised Appendix provides an interesting and useful analysis of the similarities and differences in particle deposition, retention, and dose between humans and rats used in controlled exposure studies. While many of the complexities are presented and appropriately discussed, others are either not addressed or fully discussed, such as:

- 1) The substantial differences in intra-airway distribution of instilled and inhaled particles.
- 2) “no net absorption or secretion of mucus during transport” (p. 7A-8, lines 17 and 18). This statement is clearly incorrect.
- 3) An inconsistent use of ICRP, 1994 assumptions, e.g., not using its two-compartment bronchial region clearance, while using its three-compartment alveolar region clearance rates.

Despite the somewhat arbitrary decisions incorporated in the MPPD model, the human-rat comparisons were made using the same variables for both species, and can be considered to

be useful and informative in understanding the applicability of published animal experiment data to the interpretation of human health risks.

Specific Comments

<u>Page</u>	<u>Line(s)</u>	<u>Comment</u>
7A-3	25	I challenge the statement: “For instillations into the lung, the dose can be characterized fairly well.” Does this mean the “delivered dose”? It is necessary to caveat such a statement, acknowledging that the dose distribution in an instillation is highly nonuniform and brings PM into dependent airways without the preferential deposition at bifurcations and in centrilobular airways that occurs with inhalation.
7A-6	24	change “(RIM)” to “(RIVM)”.
7A-10	18	insert “most” before “humans”.
7A-10	28	change “monopodial” to “monopodal” here and in subsequent usage.
7A-11	5	insert “related lung ventilation” before “level”.
7A-14	7&8	This sentence should be deleted. There was a typo in the HEI report that was cited, leading to the misinterpretation here.
7A-50	21	change “is effected” to “onset is determined”.

Chapter 8 of PM CD, Draft 5

General Comments:

As befits a fifth iteration, this draft provides a thorough and balanced review of a very large literature of observational studies of associations between ambient particulate matter concentrations, compositions, and particle size distributions and human health effects. It also provides quite thorough and balanced discussions of the adequacy and interpretability of models and exposure-response relationships that have been used to describe the associations and their strengths and limitations. The section on exposure characterization error is a particular strength on an issue that really needed a more thorough and dispassionate analysis than was previously available.

In my view, Chapter 8 now warrants CASAC endorsement and closure.

Specific Comments:

1. page 8-51, line 30: change “Detroit” to “Detroit Metropolitan Area” or to “Windsor, Ont, adjacent to downtown Detroit”
2. page 8-60, line 19: change “at” to “below”
3. page 8-291, line 21: clarify the meaning of “more sensitive”
4. page 8-292, line 27: change “PM^{2.5}” to “PM_{2.5}”
5. page 8-306, lines 7-15: This whole paragraph is much too speculative. Delete it.
6. page 8-315, line 2: change “merely” to “solely”

Chapter 9 of PM CD, Draft 5

General Comments

This revised chapter now warrants the title of “Integrative Synthesis”. It is clearly written and successfully draws forward the most important elements of the preceding chapters that should inform subsequent decisions affecting the selection of NAAQS for PM. It is, however, too long, and would benefit from condensation by about one third to one half, with notes that the details are available in the preceding chapters.

I agree with Dr. Crapo that Figures 9-1 and 9-2 leave the impression that 2.5um is an inappropriate cut size for fine particulate matter. It would be much better to illustrate the minimum in the size-mass continuum with data more representative of typical urban and regional aged air masses in relatively humid climates where aging and hygroscopicity lead to larger aerodynamic particle size minima.. The discussion of these issues should also provide more of the background that contributed to the selection of 10 and 2.5 um as cut-sizes, and that it was

recognized that they were selected, at least in part, as conservative choices from a public health protection standpoint. A somewhat smaller cut-size than 10um would probably better represent average penetration into the thorax, and a somewhat smaller cut-size than 2.5um would better represent the minimum for dry air conditions and freshly generated PM, but they would be less public health protective for conditions and people at the upper bounds of normal variations. In this context, they remain prudent choices for NAAQS criteria.

I was particularly impressed with the synthesis of the evidence in Sections 9.2.3.2.7 on “Inhaled particles as potential carriers of toxic agents,” and 9.2.3.2.8 on “Coherence of evidence”.

The Section 9.2.3.2.7 text on particle bound water provides a framework for addressing the apparent paradox of having a substantial epidemiologic database exhibiting significant health responses to current ambient PM exposures and a rather meager supporting literature from toxicology. While most of this section draws its evidence from physical chemistry considerations, and therefore not from Chapter 7 on toxicology, which is appropriate for an integrative synthesis, it does cite one important toxicological study, i.e., Morio et al. (2001), a study not cited in Chapter 7. I therefore strongly recommend that Chapter 7 be revised to feature this study and to briefly summarize that part of Chapter 2 that provides a basis for the Morio et al. (2001) study. I would also like to see a broader discussion of particle bound water in Chapter 9 and in earlier chapters, including its influence on positive artifacts in mass concentration measurements, and on chemical transformations within airborne particles.

Section 9.2.3.2.8 on the coherence among the human population studies, and of the epidemiology with the relevant toxicological studies, provides a concise and important summation of the overall biological plausibility of adverse human health effects caused by exposures to ambient air PM, and provides important support for NAAQS that provide

equivalent, or perhaps more stringent, public health protection than the current suite of PM NAAQS.

Specific Comments

<u>Page</u>	<u>Line(s)</u>	<u>Comment</u>
9-19	2	“known” is misspelled.
9-19	7	insert “exposures” after “short-term”.
9-19	11	There have been no studies in “Central America”. The authors presumably were referring to studies in Mexico, which is in North America.
9-23	14	change “PM _{2.5} ” to “PM _{10-2.5} ”.
9-24	5	change “Figure 9-5” to “Figure 9-6”.
9-25	12	insert “, Ito, 2003” after “Lippmann et al., 2000”.
9-51	8,9	bifurcation “hot-spots” are not limited to the “TB tree” but also occur on bifurcations of respiratory bronchioles and alveolar ducts, as demonstrated by Brody, Warheit and their colleagues.
9-51	1	“inhalation” and “CAPs” should be transposed.
9-62	20	change “larger” to “smaller”.
9-90	30	add “Gauderman et al., 2002 and Avol et al., 2001” as support for the statement.

Dr. Joe Mauderly

Review of Chapter 7, PM CD

Mauderly

General Comments

Overall, the chapter is improved from the last draft. Numerous previous content issues have been resolved, and the text is much cleaner. The issue of exposure-response could still use some tuning up.

Specific Comments

P 7-8, L 9: Is there a reference for a study showing that cardiovascular effects can be due to direct PM uptake into the blood, or is this just a recitation of hypotheses?

P 7-8, L 17: It's not the oxygen-carrying "capacity" of the blood, in any conventional sense, it's the reduced blood flow.

P 7-17, Table 7-2: Here and in following sections, the city is used as a descriptor of ROFA. This isn't useful. While city might be a somewhat (if questionably) useful descriptor of CAPs, ROFA varies in composition from plant to plant and from feedstock to feedstock. Our own experience demonstrated that two samples of "Boston" ROFA from two units of the same plant at two different times had different compositions and biological effects. I recognize the difficulty of describing ROFA – in fact the original papers typically provide very poor descriptions. However, using the city is both meaningless and misleading.

P 7-77, L 21: By definition (and in the study cited), semi-volatile materials are in both the PM and vapor phases. It should be "—PM and vapor-phase semi-volatile —".

P 7-153, L 25-28 (and entire section 7.7.1.1): Understanding dose-response, and the extent to which we can determine it from present data, is important. This section makes an attempt to address previous calls for a summary of the subject, but needs some tuning up.

The Ghio et al., 200a citation is a good example. The present statement does not say, but the wording implies, that increases in fibrinogen were observed at $23 \mu\text{g}/\text{m}^3$, which is not true; however, the study did yield some very useful perspectives on exposure-response. Those ought to be described. First, it should be stated that any comparisons using exposures to CAPs at different times do not comprise a true dose-response study – CAPs are not identical from day to day. Moreover, any study that does not expose the same individuals at different levels (Ghio did not) cannot be a true dose-response study. Given that, if you are going to cite the study in this perspective (which I recommend that you do, with appropriate caveats), there is more to be learned from it than you report. Ghio et al. divided their exposures into three groups (tritriles) with a fourth group as controls. They did not find a progressive

exposure-response relationship for fibrinogen, but they did find fibrinogen to be increased slightly for all tritiles of exposure. They wrested statistical significance from the response only by lumping all exposure groups – which is fair game – but the slight increase was observed even at the lowest exposure tritile, which was a mean of $47 \mu\text{g}/\text{m}^3$. Even given the caveats, that’s an important perspective. Moreover, they found a progressive increase in BAL neutrophils with exposure, and again, the increase clearly started at $47 \mu\text{g}/\text{m}^3$. This latter finding isn’t showcased in this section, but is more important than most of the factoids that are.

The Godleski et al. (2000) paper, on the other hand, doesn’t give results in such a manner that one can infer exposure-response relationships between total CAPs and responses. They show regressions with components of CAPs and eke out some significant relationships. However, stating that they found significant effects at CAPs exposures from 100 to 1000 $\mu\text{g}/\text{m}^3$ is misleading. They found effects from exposures that encompassed that range, but the paper gives no indication of the lowest exposure level producing significant (or strongly suggestive) effects. The study was useful, but not for this purpose.

The point is that when discussing exposure-response relationships and LOELs, it is misleading, if not outright disingenuous, to cite significant effects across a range of exposure concentrations without citing the concentrations that caused the effects. If the cited report doesn’t let you do that, then it’s not a useful citation for this section.

P 7-159, L 1: These are exposures, not doses.

P 7-166, L 6 and Table 7-14: It is true that the Ghio et al. (2000a) study showed that exposure to CAPs at a mean of $120 \mu\text{g}/\text{m}^3$ cause more than a two-fold increase in BAL PMNs (they called them neutrophils). However, the more meaningful information is that the increase began at a mean of $47 \mu\text{g}/\text{m}^3$.

7-186, L 3 – 7-187, L 17: Although the information here isn’t wrong, it pertains to coal “smokes” that have little, if any, relevance to components of coal emissions to which the public is exposed in the U.S. If the examples are going to be retained, a sentence should be added to make this clear.

7-187, L 19: The section on mutagenicity of mobile source emissions says nothing about emissions from natural gas-burning engines. There are now multiple reports indicating that natural gas emissions are also mutagenic. Although some are more recent than the cut-off date for the CD, an earlier paper that could be used as an example is Lapin et al., Mutation Research 519: 205-209, 2002. I’m not suggesting a big section on natural gas, but a paragraph indicating that such data exist and such emissions have mutagenic activity would be appropriate.

P 7-197, L 15-18: As written, this sentence doesn’t make sense. The paper reported that the mutagenicity of the “cold diesel” sample was decreased by addition of S-9. The sentence left out the S-9 part.

P 7-201, numbered list: One of the key contributions of toxicological studies (if they are so designed) is information on exposure-response relationships. While it's true that few of the studies cited in the chapter were designed to accomplish that, the point certainly belongs in a list of what role toxicological studies "can play".

P 7-210, L 32, and next page: The organic fraction is part of PM. If the organic fraction came originally from collected PM (as is the case for nearly all citations in this section) it is not appropriate to speak of the organic fraction as if it were something other than PM. You can talk about the extracted organic fraction of PM vs the rest of the PM, but they are both "PM".

P 7-217, L 14: "Dosimetric" should be "dose metric".

P 7-218, L 24-25: You say "several" controlled human exposure studies provide interesting findings, but you cite only two, and neither of them provide much insight into the relative roles of PM and co-pollutants. If you include all studies in which humans were exposed to mixtures of PM and co-pollutants, but don't test their relative roles, then there are several more.

P 7-219, L 5: Here, six studies are a "few", but on the previous page, two studies were "several".

P 7-221, end: You are missing a "bottom line". You've gone through a recitation of an assortment of studies using "susceptibility" models, but are any summary conclusions to be drawn from the collection?

Review of Appendix A, Chapter 7, PM CD

Mauderly

General Comments

The appendix is somewhat improved, but remains denigrated by containing comparisons that, while perhaps mathematically correct, are seriously flawed in concept. Calculating that a rodent exposure to a single-mode aerosol would have to be very high to achieve deposited or retained doses similar to those achieved by humans exposed to multi-modal aerosols at the roadside is simple not helpful. No human is exposed to that material in those multiple modes. We do not need a dosimetric appendix if its conclusion is that, if one only picks the right mathematical comparison, any dose can be justified. We already knew that.

The appendix contains information on comparative biological responses that belongs in the main body of the chapter. It is exactly for the purpose of making sense of comparative responses that the comparative dose modeling is required. The purpose of the appendix is to provide a foundation for judging the value of animal data and comparing animal and human responses in the body of the chapter. The health response comparisons belong there, not here.

Specific Comments

P 7A-1, L 26: It should be “—equivalent to those —”.

P 7A-2, L 15: It should be “—use of these —”.

P 7A-3, L 10: This is only true if you believe (or hypothesize) that the effect is due to retained dose, rather than the most recent dose. Some effects probably are, and some probably are not. If the statement is strictly true, then the interpretation of the time series studies must be wrong. If so, and because all humans are exposed chronically, how could effects be ascribed to only the most recent dose?

P 7A-3 L 25: It should be “—the total dose—”. You can’t characterize regional doses (e.g., TB vs A) at all.

P 7A-6, L 21: “Disposition” ordinarily also includes translocation within the organ. Does “clearance” in this appendix mean only removal from the organ?

P 7A-6, L 24: It should be “RIVM”.

P 7A-8, L 11: Again, does “clearance” here mean removal from the alveolus, or removal from the organ. Material can be removed from the alveolus and still be in the lung (interstitium, lymphatics, capillaries, etc.).

P 7A-8, 20-22: Of course, it is known that mucus does not flow evenly up all airway surfaces. Indeed, “streaming” of mucus and the PM it carries is a well-known and almost universal phenomenon. Hopefully, the modelers know this, but it should be mentioned as a caveat.

P 7A-9, L 7-8: According to the dissertation on overload, as reflected in Table 7A-13, even the lowest of these exposures exceeds “overload” and the higher two are well beyond “stasis”. Why would one select for the MPPD model alveolar clearance rates that are thought to reflect “overloaded” kinetics? Moreover, why should we believe the model results for cumulative lung burden if they are all based on “overloaded” clearance kinetics?

P 7A-9, L 21: The relevance of the point is not clear. Why would one worry about 10-minute computations on one computer when many people have spent over a year reviewing and revising this chapter?

P 7A-11, L 26-28: Why would one introduce a peculiar terminology for PM size in this chapter? Here, we have “coarse” including everything over 1.0 μm , and “accumulation mode” going downward from 2.5 μm , thus making PM_{2.5} both “coarse” and “accumulation mode”. That hardly fits with the descriptions in the remainder of the Criteria Document.

P 7A-11, L 28: Here we have an inkling of the bias to come – that rats are “normally” only exposed in certain ways (limited to PM_{fine} CAPs and resuspended ROFA). That’s pure bunk. Rats are exposed to most every size distribution imaginable – sometimes (unfortunately) including sizes they can’t even inhale! Rats are certainly often exposed by inhalation to atmospheres simultaneously containing PM ranging from well above 1.0 μm (remember, you said this was “coarse”) downward to below 10 nm. The authors can showcase the EPA ROFA studies if they like, but they shouldn’t posit that this is how rats are “normally” exposed.

P 7A-19, Fig. 7A-5: Something is wrong with the figures, the legend, or both. The time scale says “post exposure hours”. If this is retained mass after exposure, then why isn’t the mass at time zero 1.0? Only the amount of mass present in the TB region (not the “retained” mass) could increase after time zero (the end of exposure) by virtue of more entering the region from the A region than was originally deposited there. Regardless, the amount at time zero cannot be zero, as the figure shows, unless there was no TB deposition at all.

P 7A-25, Table 7A-5: The sources of the values used for alveolar surface and FRC ought to be stated explicitly. These values are critical to the modeling presented later, and the explanation needn’t be more than a paragraph. An attempt to trace the sources proved difficult and did not engender confidence. This is particularly important because the surface area values here are much lower than those that are frequently cited. If human alveolar surface is really only 57 m², then why do physiologists usually assume 70-100 m²? Rat surface is often cited at 0.4-0.5 m². Of course, the most correct value is unknown- all values are modeled estimates that involve several assumptions. The point here is not that the values are wrong – I can’t tell that – the point is that there needs to be an explicit statement of how the values were derived (the experimental and modeling foundation, not just a combination of primary and secondary references).

Yeh and Schum (1980) are cited as the source of the surface area value for humans, yet I can’t find a value for alveolar surface in that paper (airways yes, but not alveoli). That paper reports modeling data from one human lung cast at presumed TLC, and assumes the values for FRC, TLC, and number of alveoli used by the ICRP (1974) for “standard man” (2.2L, 5.6L, and 3x10⁸, respectively). Table 7A-5 calculates a value for surface area from that paper, but uses a different FRC (3.3L) and cites the RIVM report as the source. The RIVM report lists that value for FRC, and cites ICRP 1994 as the source (apparently, ICRP’s standard man grew during the ensuing 20 years). Interestingly, in the section on age effects, the RIVM report cites an FRC of 1.8L for 21 years and cites 6 different references (I don’t have time to read all of them to divine where that particular value came from). That value is lower than the one cited for 18 years (I thought you had to be over 30 to begin shrinking). The RIVM report also cites Gehr (1978) for a human surface area of 143 m². For rat surface, the RIVM report cites a Mauderly (1979) review, which cited Johanson & Pierce (1973), who reported that in Sprague-Dawley rats, it ran from 0.55 to 0.88 m², depending on age. That’s a lot higher than the value in Table 7A-5, which cites Yeh

et al. (1979) as the source. Those authors reported modeling results using data from a TLC lung cast of a female Long-Evans rat and, like the paper on the human cast, no value for alveolar surface is given. Table 7A-5 calculates a value for surface from the modeling results, and used a value of 4.0 ml for FRC, citing the RIVM report for that value. The RIVM report does use that value, but doesn't cite the source.

P 7A-26, 1st 4 lines: This information is confusing, and only partially matches with the comparisons that actually follow. There ought to be a simple, factual, list (1,2,3, etc.) of the comparisons that follow. For example, the first comparison does indeed compare rats and humans one size mode at a time (if I understand it correctly). These sentences imply that this is not done at all.

P 7A-28, 29: These two tables, and those that give the assumptions behind them, comprise the most useful material in the appendix. Unfortunately, the comparisons that follow are less well-founded, more confusing, and less helpful. One could end the appendix here and have provided a service.

P 7A-30, L 1-4: At about this place in the text, a very important concept that is completely missing from the appendix should be clearly stated. Of course, one can expose rats to PM having a size distribution including the coarse fraction in such a manner that the deposited burden is the same as that estimated for humans. It may take a huge concentration, but you could do it. However, the rats would only be inhaling the inhalable or respirable portion of the material. What that means in practical terms is that unless the material is homogenous in composition through out the size distribution one is depositing in rats a different average composition than would be deposited in humans. Not only that, but the number of particles and area of particle surface would differ between the species at the same deposited mass dose. The bottom line is that no matter what heroics you attempt in order to deposit the same mass, you will be depositing different "stuff" (on average) in the two species.

Stating this concept clearly is not only important to the discussion at hand in this section, but it is also important because it shines light on a problem that infests the rest of the appendix. For example, this concept is totally ignored in the comparison of resuspended ROFA in the rat to roadside exposures of humans. Who cares what exposures would produce the same dose? The stuff is not, and cannot be, the same. Humans don't breathe ROFA in a tri-modal size distribution at the roadside (or anywhere else). It makes no sense to compare any single material in the laboratory to environmental exposures to PM having a distribution of composition and size. Dosimetric comparisons in that case become academic exercises that have little, if any, basis in real biology. Moreover, the exercise becomes a distraction at best and misleading at worst in an appendix that is supposed to bring clarity to comparisons of animal and human study results and potential hazards.

P 7A-30-31: This and the next sections are troublesome. It's hard to come up with a scientific reason that these comparisons are included. The authors need to take off their ROFA glasses. The majority of experimental PM work over the past 40 years

did not use resuspended material. As an example, the studies used for the basis of the deposition and clearance assumptions in the MPPD model certainly did not – they used generated PM having designed size ranges, and other studies have used resuspended PM having a monodisperse size distribution. The statements about cyclones are irrelevant to either.

It is stated that it would not be appropriate to use resuspended PM to simulate human exposures or doses. That depends on the question you are asking and the design of the experiment. Of course it would be appropriate – if you are comparing exposures to and effects from the same material (i.e., apples to apples). It only becomes inappropriate if you are comparing exposures to different materials (apples to oranges, or ROFA to roadside), in which case your conceptual troubles are much bigger than your dosimetric troubles. Among the mixtures that people breathe are 2.0 μm MMAD PM having a certain composition and size distribution – perhaps like your resuspended material. In fact, people are breathing many different PMs having different compositions and size distributions – not just one material having a trimodal distribution.

It's ridiculous at the outset to think that you can do a laboratory study of a single type of PM and represent human exposures to a diverse population of PM – matching the mass, number, or surface dose is not the issue. On the other hand, if you have PM representing some portion of what people breathe, you can study that fraction, and reasonably propose that the results are relevant to that portion of the mixture that people are breathing. Conversely, if you are exposing animals to material that does not represent a portion of what people breathe, you shouldn't be worrying about doses– you are testing some hypothesis that can't be extrapolated to humans on a dose basis anyway.

(Moving on through Section 7A.5.1.4):

It is stated that it is not appropriate to compare a rat dose from one PM size fraction to a human dose from the same size fraction, because people breathe all size fractions. First, on the basis of the above rationale, that's bunk. Second, regardless of whether or not that's bunk, it is certainly not appropriate to compare a rat dose from one PM type and size fraction to a human dose from many PM types encompassing multiple size fractions. Why would one compare such doses? Implicit in the comparison is that neither composition nor size matter to toxicity. Nobody believes that. The only apparent reason to make such a comparison is to justify using extreme doses.

ROFA is a good model PM for testing certain hypotheses about soluble metals. It is ridiculous to propose ROFA as a surrogate for total environmental PM exposure – or even to total combustion-derived environmental material.

P 7A-31, L 32 and P 7A-32, L 1: The wording used here either states, or strongly implies, that human clearance is never affected by lung burden and rat clearance is always affected by lung burden. How did you come to that conclusion? I don't accept that

as a universal truth, and don't believe that there are data confirming it. Could this statement and the modeling results in Figure 7A-9 be influenced by the fact that the clearance assumptions for rats were based on source data collected only under overload conditions by the chapter's own definitions (point raised above)? Even so, the Figure suggests that slowing of clearance is only affecting retained mass markedly at exposure concentrations that are extreme (over 10 mg/m³).

P 7A-37, Figure 7A-10: The discussion of relative exposures to achieve equivalent retained lung burdens misses an important point. The point is illustrated clearly by the figure. Yes, it is possible to expose rats to 60 µg/m³ and hit at 6 months a normalized target human lung burden. However, you only hit that lung burden on the last exposure day. If the health outcome of concern responds to the lung burden, rather than the recent dose, you can probably assume that the effect is not caused by the instantaneous lung burden, but rather by a lung burden that exists over some period of time. Comparing the areas under the two curves illustrates clearly that the human and rat lung burden x time factors (similar to the concept of CxT) are very different. That is an important point that should be made in the section, not just the point that you can or cannot hit a target lung burden and how long it takes. One would have to use a constantly, or frequently, changing rat exposure concentration to mimic the time course of lung burden in humans. That could be done and would be an interesting strategy, but I'm not aware that it has been done. This fundamental point is missing from the discussion.

P 7A-38, L 6-9: Same comment as above. Again, you are only hitting this burden at the end of the exposure period.

P 7A-39, Section 7A5.1.6: The situation described has a person exposed one day to 100 µg/m³, PM₁₀ after a 10 year exposure to 64 µg/m³. First, it's not clear why one would pick 64 µg/m³ PM₁₀ as the steady state 10-year level – seems an odd number. If one is thinking in a time series mode of course, the excess exposure that day is 46 µg/m³, not 100 µg/m³. Second, you have a rat exposed for 6 months to a resuspended dust that is 50% coarse and 50% accumulation. May we presume that this definition goes back to your calling everything over 1.0 µm coarse? Third we have a human long-term exposure that was 25% highly insoluble. Did the estimate of human cumulative lung burden consider deposition and clearance of only 25% of the mass, or 100%? Was the “not highly insoluble” mass considered to clear like the rest, considered to be invisible to the computation, or what? Did the lung burden on the last day of human exposure only consider the highly insoluble part (that is, did the other part instantaneously disappear somehow)? Was the resuspended dust considered all highly insoluble? Could we then conclude that it did not have the same composition as the human exposure material (or perhaps any part of it)? If so, why are we doing this?

The authors conclude from the example that it illustrates the “complexity of using a rat model to simulate effects of PM in the human lung”. First, the example said nothing at all about effects; it focused on dose. Effects are a different ballgame that includes

a host of additional variables. Second, and most importantly, the whole example is flawed because you weren't dealing with the same exposure materials in the two species to begin with. What the example illustrates most clearly is the complexity of thinking about the use of rat models, not the complexity of simulating doses.

P 7A-41, "Caveat" section: The most important caveat is not mentioned. The quantitative accuracy of the results is a minor concern; the mathematics are probably correct and the underlying assumptions of the model may not be far off. Ensuring that these tools are used to make biologically and environmentally relevant comparisons is the much greater concern.

P 7A-41, L 25-28: This is the first time I've seen anyone propose that overloaded rats might be a useful model that represents a "sensitive" population! Here, we find such rats defined as being "highly sensitive" to PM. The proposition doesn't seem dangerous at this point – clearance is slowed in an overloaded rat, so it must be more at risk from the next inhaled particle. Later however, that gets translated into a potentially useful model of human sensitivity. If we follow that logic, then all of the past studies involving overloaded rats were just ahead of their time – they were studies using models of increased human susceptibility! EPA should have had the foresight to set a unit risk factor for diesel-related lung tumors from the rat data – those were studies of a sensitive population!

P 7A-45, L 6: What do you mean "strictly speaking"? The analysis was flawed – period.

P 7A-45, L 9-10: By assuming that all PM₁₀ is insoluble, this comparison is flawed from the get-go. In the last sentence, it's not clear whether you mean "comparable surface dose" of the total PM, or just the insoluble part. This kind of apples & oranges comparison isn't useful

P 7A-45, L 26 – P 46, L 21. The presentation of biological results of studies and human-animal comparisons of responses is out of place in this appendix. This is a dosimetry appendix. Given all the other variables in the comparison, whether or not you happen to get similar responses in the two species doesn't confirm or deny the similarity of dosing. The comparative responsiveness of humans and animals is another issue, and belongs in the body of the chapter. Moreover, on lines 46, 12-15, you decide to ignore PM clearance (which one really can't) and don't say whether the comparison is for the extract or the total PM. The comparison is so cloudy as to have no real value.

P 7A-56, L 11: Again, it is not scientifically sound to justify high level exposures to resuspended PM on the basis of simulating doses from multi-modal environmental PM.

P 7A-57, L 1-6, and 57, L 22-58, L 8: Again, presenting health data is out of place here. You need to address the similarity or difference in response between species in the body of the chapter. Comparative dosimetry is one piece of information needed to do that

job, thus, the reason for this appendix. However, suggesting here that comparable biological responses confirm similar dosimetry is circular reasoning.

P 7A-58, L 17-20: Overloaded rats may be models for overloaded humans, as long as the mechanisms of “sensitivity” are the same. The broad wording here suggesting that overloaded rats may be useful models for “decreased pulmonary defenses” is an overstatement. I have a problem with promotion of this concept, unless you are limiting it to simulating humans in whom defenses are specifically impaired by PM overload.

Comments on Chapter 9

Mauderly

General Comments

For the most part, this integrated synthesis is a reasonable start – but only a start. The job isn’t done yet. At the Panel’s recommendation, staff developed a review of (what the reader must suppose are) the most important conclusions from foregoing chapters. This is a reasonable approach, if the rest of the job (a true integrating synthesis) is done. On the other hand, the chapter reviews could be left out altogether and only a truly “integrative synthesis” presented. The chapter does not yet present a succinct, clear, synthesis across chapters that shows how the different types of information can be related to frame the most important findings related to standard setting.

It is not clear that the most important knowledge is brought forward. It is clear that some information is brought forward that seems to be of secondary or tertiary importance. An example is the speculation (without confirmation in that particular study) about the chemical species that might have been responsible for bacterial mutagenicity of collected engine emission samples. The point is not that the speculation was wrong – it was a reasonable sidebar speculation in a discussion section of a recent paper, and one that was a good bet on the basis of previous confirmations by bio-directed fractionation two decades ago. The point is that it is a mystery why that particular factoid is “cluttering up” what is supposed to be a focused synthesis of the most important facts and conclusions bearing on the PM NAAQS. Indeed, the aforementioned speculation had little to do with even the most important conclusions of that particular paper.

I would prefer that the chapter conclude with a section summarizing the most important points supporting judgments about the PM NAAQS. If not the entire chapter, then as least a final section, ought to make clear what the science says (or can’t yet say) about the indicator, level, averaging time, and statistical form of PM standards. The authors need not fear usurping the role of the Staff Paper. The section wouldn’t draw conclusions regarding the components of the standards, but it could point toward the knowledge having the greatest bearing on each of the components.

Specific Comments

P 9-7, Figure 9-1: This is a venerable figure, but it needs to be updated to reflect the terminology described in the text. The term “ultrafine” is used in the text, but appears nowhere on the figure.

P 9-8, L 11: It is stated that progress has been made in measuring diesel particles. Isn't the progress in regard to measuring carbonaceous PM per se? Why just diesel particles?

P 9-9, L 13-14: The wording implies that ultrafines don't penetrate readily because they deposit to surfaces. Ultrafines are defined in the chapter as equal to or less than 100 nm. Figure 9-3 suggests that some PM in this size range should have a high penetration factor.

P 9-17, L 19-21: We still have only a cursory understanding of the potential health importance of ultrafines. We know enough to know that it's plausible that some of them may be important health concerns, but we don't know if this is true. I'd strongly recommend waiting until we have more data produced by systematic laboratory studies before investing in an ultrafine sampling network. That's a huge investment on the basis of very skimpy data. The data at this time are suggestive, but largely anecdotal – few systematic studies have been done.

P 9-39, L 7: “SO2” should be “SO₂”.

P 9-39, L 24: This is a silly sentence. How could it be possible that effects of PM₁₀ are not due to its constituent components? Could the effects of PM₁₀ be due to something that isn't in PM₁₀?

P 9-41, L 12: “Finds” should be “findings”.

P 9-42, L 29: Why emphasize that these are “powerful” techniques? The following line emphasizes their weakness. Why are these techniques called powerful, and others throughout the chapter are not? What's the point?

P 9-49, L 27-28: One of the main reasons that non-inhalation dosing is used is that inhalation exposures typically require large samples. That ought to be mentioned.

P 9-53, Table 9-4: This comparison is seriously flawed because the exposure materials were not the same. You might play with such a comparison (with substantial caveats) in an earlier chapter, but the comparison is not sufficiently scientific to showcase in a summary chapter.

P 9-54, L 27: As noted in the preceding source chapter, this manner of presenting the information is misleading. Without further knowledge, the reader takes the statement literally to mean the effects were observed at the lowest concentrations listed. This is not true.

- P 9-55, L 10: It should read “inhalation exposures to ROFA”.
- P 9-56, L 28: See comment for 9-54, L 27. Again, the presentation is misleading.
- P 9-57, L 1: Ditto.
- P 9-57, L 11: It should be noted that the exposures were by instillation. Otherwise, the reader will assume that they were by inhalation.
- P 9-59, L 10: Isn't the “condensate” fraction part of PM? If it's something else, make that clearer.
- P 9-59, L 13: As noted in comments on chapter 7, if you are going to refer to the “coal smoke” results, you should put in a few words making clear to the reader that this is something different than the material to which people are exposed in the U.S. The problem is that if you don't, most readers will assume that the conclusions pertain to coal-fired power plant emissions. That would be misleading.
- P 9-59, L 17-18: The wording suggests that the referenced study determined that the mutagenicity was caused by these chemical classes. That is not true. The authors speculated in the discussion on the basis of differences between tester strains and +S9 that these classes might have been responsible. The speculation may or may not have been correct, but it certainly isn't something sufficient to bring forward into a Criteria document summary. In fact, the chemical classes responsible for the mutagenicity of such samples was pretty well defined by bio-directed fractionation in the 1980s.
- P 9-62, L 3-2: This statement in isolation doesn't help much. Give another sentence or two that explains the evidence (e.g., what you mean by “low” concentration).
- P 9-72, L 13: Why include this factoid? Of what relevance to the integrated synthesis is it that you might be able to instill enough ROFA to kill a rat?
- P 9-73, L 11-17: This paragraph probably doesn't belong in an integrated synthesis. It isn't an update of real knowledge, it is just a recapitulation of an old hypothesis that hasn't been tested in any thorough way. We know that some PM can travel through the circulation. We still plausibly speculate, but still don't know, if such can affect heart function.
- P 9-96, L 1: Being exposed to a higher concentration isn't a “susceptibility” factor in any conventional sense. Receiving a higher dose because a lung disorder caused enhanced deposition is a dose-related susceptibility factor, but just being exposed to high concentrations is not increased susceptibility. This is a new use, or misuse, of the term.
- P 9-99, L 22-27: The paragraph is not helpful unless the comparison is completed. You give relative risks and exposures for the London fog, which isn't relevant to the synthesis, but you don't bother to give a risk factor or an exposure level for a current scenario.

P 9-100, L 2: Are this total or non-accidental deaths?

P 9-107, L 22: Define “occult” deposition. Not all readers will have read the relevant preceding chapter (assuming that you defined it previously).

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July 14, 2004

Comments on Chapter 7, “Toxicology of Particulate Matter in Humans and Laboratory
Animals”
and
Chapter 9, “Integrative Summary,” June 2004 Draft

Roger O. McClellan

The following comments are provided on the two revised chapters.

A. Chapter 7, Toxicology

General Comments

- 1) In general, this revised chapter represents a substantial improvement over the earlier drafts. However, there are certain areas in which further improvements are needed to provide a chapter suitable for closure.
- 2) A major shortcoming of the chapter is the lack of a contextual basis for the total chapter and the appendices. Specifically, the authors do not provide a basis for the reader understanding how the findings reported in the chapter will be useful in establishing the four elements of a National Ambient Air Quality Standard (NAAQS), namely, (a) the indicator(s), (b) averaging time(s), (c) numerical level(s), and (d) statistical form(s). I would argue that the information contained in the chapter is probably of limited use for decision making on any of the elements. However, one will never know unless the authors address the four elements. Perhaps the strongest case could be made with regard to identifying “indicator(s).” Even with regard to indicator(s) the chapter falls short. Thus, the reader is left with a single broad conclusion after wading through 350 pages of material – “Some kinds of particulate matter (PM) in some particle

sizes and with some chemical characteristics, when inhaled by humans at sufficiently high concentrations and for sufficiently long periods of time may cause an increase in adverse health outcomes.” As meager as this conclusion may appear if it were flushed out it could provide information that would help in setting the PM NAAQS and in identifying future research needs and the limits of toxicology in addressing these needs.

3) Section 7.1.1 - “Methodological Considerations” provide a useful, but limited as noted above, context for this chapter. I especially appreciated the identification of a number of important caveats or limitations that must be kept in mind in interpreting the findings reported in the chapter.

4) One important caveat that needs discussion in Section 7.1.1 is the issue of statistical considerations. The entire Criteria Document, and especially Chapters 7, 8, and 9, need to be more forthright in describing the very weak signal for increased health effects statistically associated with small increases in various PM metrics. The increases in health effects that have been observed are very small increases above the very low background rate of adverse health outcomes that are statistically distributed (see Chapter 9, pages 95-100). Indeed, it is apparent that statistically significant increases can only be found when the number of observations are very large in terms of the human population studied and the “delta” of the change in PM metric is large. Based on the above “facts” I would argue that most, if not all, of the experimental studies lack the statistical power to describe changes that are relevant to human populations at ambient levels of PM currently encountered in the U.S. The experimental designs used are largely relevant to studying deterministic outcomes rather than stochastic outcomes.

5) A careful review of the chapter reveals that even with flawed experimental designs (that usually involve an inadequate number of subjects, a lack of multiple exposure/dose levels, a lack of long-term observations and a lack of comparison between treatments) it is apparent that PM is extraordinarily heterogeneous as to its size distribution and chemical composition and, moreover, there are marked differences in the potency of different kinds of PM for producing an increase in adverse health effects. The chapter needs to clearly state this conclusion which has profound implications for setting and implementing a NAAQS for various PM indicators that will yield positive health benefits. Indeed, the only conclusion one can draw is that the current approach using an indicator defined by size, without regard to chemical

composition, is likely flawed and results in substantial societal costs and may not always have associated health benefits.

6) Appendix 7A – “Rat to Human Dose Extrapolation” while improved over the earlier version is seriously flawed in “over-selling” a product and attempting to justify much of the animal research reported in the body of the chapter. The chapter is an interesting exercise in modeling. However, models are only that – models of reality – and need rigorous validation. I would characterize the Appendix as providing a sound basis for model validation. The chapter would be substantially improved by clearly identifying the very few observations that provide the basis for extensive mathematical extrapolations. I am very aware of how limited the biological inputs are since many of them originated in research programs I directed.

All of the calculated values are presented with a high degree of precision (two or three significant figures) and only rarely with an indication of uncertainty in the results leading the unwary reader to perhaps over-interpret the results presented. It should be recognized that the results are based on model calculations and in the absence of further validation should be used and interpreted with caution. I suggest that all of the table and figure captions be reviewed and the words “estimated” or “calculated” placed in front of any estimated or calculated quantities.

The Appendix would be substantially strengthened by including “measured” values for comparison with “calculated” values. For example, “measured” lung burden data from the study of Ronald Wolff *et al* (1987), [Alterations in Particle Accumulation and Clearance in Lungs of Rats Chronically Exposed to Diesel Exhaust, Fund. Appl. Toxicol. 9: 154-166] of rats clinically exposed to diesel exhaust could be plotted in Figure 7A-8.

Specific Comments

Pg 7-69, lines 16-18: This sentence does not need qualification – i.e. “the relatively recent new studies” – it should simply state – “There is little evidence for acute or chronic exposures to aqueous acid aerosols contributing to acute respiratory effects on chronic lung pathology, except a much higher than current ambient levels.”

Pg 7-69, lines 23-25: This sentence is a gross over-statement that needs qualification, i.e., non-cancer effects are observed with high levels of exposure. For example, see pg 7-70, line 24 –

Pg 7-74, lines 12-17: This conclusion is not supported by the text.

Pg 7-102, lines 30-31: This important conclusion stands in sharp contrast to other comparisons made elsewhere.

Pg 7-126, lines 5-6: This short but important conclusion needs to be linked to the statistical limitations of toxicological studies I noted earlier.

Pg 7-143, lines 18-22: The fable of particles serving as effective carriers for formaldehyde is simply that – a fable. See paper by Simon J. Rothenberg and colleagues who demonstrated, based on the physical chemical characteristics of formaldehyde, that the particle associated “dose” is insignificant compared to the vapor associated “dose.” . [Simon J. Rothenberg, Paul A. Nagy, John A. Pickrell and Charles H. Hobbs, “Surface Area, Adsorption and Desorption Studies on Indoor Dust Particles,” *Am. J. Hyg. Assoc. J.* 50(1): 15-23, 1989]. Yes, formaldehyde absorbs to particles. However, the quantity of formaldehyde delivered to the pulmonary compartment by deposited particles was calculated to be less than 1% of the quantity delivered to the upper respiratory tract.

Pg 7-152, line 11: Remove the term “greatly,” the evidence for modification of effects indicates it may occur but it is hardly supportive of “greatly modify.”

Pg 7-182, lines 23-30: In my opinion, the authors over-interpret the evidence. Yes, some ambient air particulate matter is mutagenic. However, the levels of mutagenicity measured are remarkably low.

Pg 7-192, lines 1-12: The discussion of the work of Driscoll *et al* (1997) needs to indicate that the “oxidative damage” of carbon black particles appeared to be a threshold exposure dose-response phenomena.

Pg 7-196: The experimental design of the Strandell *et al* (1994) and Seagrave *et al* (2002) studies should be more fully described. As I recall Strandell *et al* studied only particulate emissions, Seagrave *et al* studied both particle and vapor phase emissions. The same consideration applies to the Rannug (1983) study which, as I recall, focused on particulate emissions. It is not possible to compare different emission sources without considering total emissions.

Pg 7-206: This page is loaded with speculation. The discussion of the paper of Kleinman *et al* (1998) inappropriately implies a linkage between PM-hypoxygenation-angina and further adverse cardiac effects. This is totally speculation. If the authors wish to discuss CO and hypoxygenation and times to onset of angina they should reference the results of the classic HEI multi-center CO study. The next paragraph describing a study in which blood oxygen levels were never measured is total speculation and leads one to question the scientific objectivity of the authors on other matters.

Pg 7-210, lines 20-24: What a mouthful! Why not say – The Pope *et al* (2002) analysis of the American Cancer Society longer-term database provides evidence for chronic ambient PM exposure being associated with increased risk of lung cancer. The Pope *et al* study is certainly not strong evidence. Indeed, alternative interpretations related to the weakness of smoke history data leads to legitimate questions as to whether there is a PM-lung cancer effect.

Pg 7-212, lines 1-3: I question whether the qualitative analyses of mutagenicity for different fuel types is warranted without substantially more details as to what is being ranked here or elsewhere. Indeed, I view a ranking based on type of fuel as being very misleading. These rankings are more a ranking of the inefficiencies of the combustion processes studied in specific particulate experiments rather than inherent characteristics of the fuels. For example, a majority of the references to coal combustion are based on studies of coal being used for cooking and heating in poorly ventilated rooms in China. Yes, this is coal combustion but it is hardly representative of a modern coal-fired electrical power generating plant.

Pg 7-216, lines 5-18: This paragraph overstates the strength of the evidence for diesel PM exacerbating allergic responses to inhaled antigens. The quantities (dose) of diesel PM or extracts studied, the sources of the test material and the mode of administration all raise serious questions as to the relevance of the findings to particulate matter exhaust from modern diesel engines. The same statement applies to pg 7-221, lines 20-25.

B. Chapter 9, Integrative Summary

General Comments

1) In general, the draft chapter provides an adequate summary of key “air quality criteria” for establishing the National Ambient Air Quality Standard (NAAQS) for Particulate Matter. However, as detailed below it is my professional opinion the chapter can be improved with some changes and additions are shortening.

2) As I have previously noted, I think it is important for the criteria document, as a whole and certainly the summary chapter, to clearly indicate the relevance of the science being reviewed to the four specific elements of a NAAQS; namely, (a) the indicator(s), (b) averaging time, (c) numerical level, and (d) statistical form. The organization and content of the present chapter does not adequately review the science relevant to decisions on these four elements. Thus, by default, the Agency (and CASAC) is leaving critical consideration of all four elements to the more policy-oriented Staff Position Paper.

3) From an organizational standpoint it is my opinion that the chapter would be improved if very early in the chapter there was a section summarizing knowledge on historical and current ambient concentrations of the several PM indicators and summary information on chemical composition. This section would provide useful background information that would provide a contextual setting for the rest of the chapter. This section could be followed by the background health data now presented on pages 9-95 to 9-100.

4) Building on the information presented above the chapter would be improved by including a brief section describing how the epidemiological evidence is based on the use of relative risk models and the critical importance of the baseline prevalence of cardio-respiratory disease in determining estimated absolute risk associated with air pollution.

5) It is remarkable that the chapter could be written with only a single sentence acknowledging the role of cigarette smoking as the single most substantial risk factor determining the “susceptible” population for PM-associated excess disease. Pg 9-19, lines 17-19: “The etiology of most air pollution related health outcomes is highly multifactorial and the important ambient air pollution exposure on these outcomes may be small in comparison to that of other etiological factors (e.g., smoking). This could well be the lead sentence in the Summary Chapter.

6) In my opinion, the chapter would be improved by more directly addressing the issue of establishing PM size, mass-based indicator(s) without consideration of chemical composition. These mass-based indicators are selected by default, they are simply the best we have in the absence of science to the contrary. In many places, the summary notes that PM is heterogenous with regard to chemical composition and there is substantial evidence indicating that PM is equally heterogenous in potency. Unfortunately, our ability to link chemical composition and toxic potency is scientifically inadequate.

7) It would be appropriate for the chapter to note that as more PM speciation data become available and is used in epidemiological studies, it will be possible to evaluate the relative health protection provided by mass-based versus chemical based indicators. Likewise, as more continuous monitoring air quality data become available, it will be possible to evaluate the relative health protection provided by standards for indicators with different averaging times and associated statistical forms.

8) I think the chapter could be substantially reduced in length without any loss in scientific content. The chapter would benefit from “heavy-handed” scientific editing by a single editor to provide a more consistent presentation. The current uneven nature of the presentation is apparent in the summaries that range in length from a short paragraph to two pages.

9) In performing the final editing, it will be important to strive for a more balanced scientific presentation that even-handedly describes the evidence for PM-associated health effects and the associated strengths and weaknesses. It is important that the science-based criteria document avoids a tone that advocates or justifies a particular standard including past or anticipated actions of the Agency.

Specific Comments

Eliminate Figure 9.2

Pg 9-11, Discussion of Figure 9.3: Emphasize that “infiltration” is strongly influenced by “climate” and, equally important, the nature of building ventilation.

Pg 9-13, Section 9.2.1.2.3, Figure 9-4: Discuss the extent to which this figure is based on modeling of “monodisperse” particle sizes. It should note that the real world is “polydisperse” and, thus, for any real world situations there is a translational issue.

Pg 9-23, line 14: This should be PM_{10-2.5} rather than PM_{2.5}.

Pg 9-26, line 12: If the Laden *et al* (2000) paper is to be cited, it is appropriate to reference a paper that provides an alternative analysis with different conclusions. (Grahame, T. and Hidy, G., "Using Factor Analysis to Attribute Health Impacts to Particulate Pollution Sources," *Inhal. Tox.* 16 (Suppl. 1): 143-152, 2004).

Pg 9-38, lines 16-20: I think this statement is much stronger than warranted based on the strength of the evidence and the challenges faced in evaluating exposure-response relationships. This represents one of the key conclusions in the CD and, thus, it must be accurate and appropriate caveats added as to the strength of the evidence.

Pg 9-49 through 9-53: This section on dosimetric considerations, including consideration of Appendix 7A, should be substantially shortened. A shortened version should emphasize the extent to which the mathematical dosimetric models have only been validated to a very limited extent. The results of the modeling exercises should be used with more caution than suggested by the material presented on these four pages.

Pg 9-95 to 9-100: This excellent section on baseline health statistics should be moved forward in the chapter as recommended earlier. It would be appropriate to indicate, and perhaps illustrate, the significant regional differences in the various health indices and some of major underlying demographic factors. In this section, it would be appropriate to repeat the statement made on pg 9-19 noting the important role of cigarette smoking as a risk factor in several of the key cardio-respiratory diseases of concern for being impacted by PM.

Dr. Günter Oberdörster

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

This chapter is quite improved compared to the previous draft, the reorganization looks good and new sections fit well into this chapter. I have a few comments that can easily be considered and should not — in my view — delay coming to closure on this chapter.

Section 7.1.1 Methodological Considerations is a nice addition as an introduction to this chapter. These are very good comments and thoughts on the concepts of PM toxicity. I would suggest on page 7-3 to include the concept of hypothesis-generating studies — which could be many of the high dose studies to identify mechanisms — and contrast these with studies of relevant low doses to test a specific hypothesis. This will provide some justification for many of the high dose studies that have been generated.

Also, I suggest to address the notion that not every small or slight response — e.g., inflammatory cell influx — to be considered adverse, rather one should differentiate between a normal adaptive or physiological response as opposed to toxic response.

Page 7-8, line 11: I suggest as an introduction to the figure to mention briefly the two pathways outlined in the figure: These mechanisms involve either the ANS or direct effects on the endothelium.

Lines 16/17: What is the heart oxygen carrying capacity of the blood? Is meant here: Decreasing blood flow?

Page 7-11, line 2: How is “blood chemistry” related to coagulation? Perhaps it is better to state: “effects on endothelial function”.

Page 7-14, line 9: The MCT model is described here as a model of COPD in humans. However, this is not a chronic but a very acute injury and it is questionable as to whether it resembles COPD.

Lines 24-28: The mostly very high doses of the studies in tables 1 and 2 should be mentioned here.

Page 7-15, Table 1, first entry: An estimated total dose is given here, is it deposited or inhaled dose? This is not made clear in the text or here.

Page 7-33, line 21: The elevated heart rate was found in which exposure group, the highest only?

Page 7-35, line 7: Additional information to include here and which would be useful is a study by Terashima *et al.* (2001; BAL induces an increase in peripheral blood neutrophils and cytokine levels in healthy volunteers and patients with pneumonia, *Chest* 119: 1724-1729) showing that simply BAL performing in humans also induces acute phase responses and release of bone marrow stimulation, whereas bronchoscopy alone does not.

Line 26: Add that carboxylate particles have a negative charge and amine coated particles have a positive charge.

Page 7-36, line 9: Emphasize also that all these studies were performed in healthy subjects.

Page 7-51, Table 6: Since these are all intratracheal instillation studies, there would be no need to have the column Exposure Technique; also, change “concentration” to “dose” and delete in the other column “Exposure Duration”, which will be only a second or so and is not needed here for instillations.

Page 7-55, Table 7: Add to the column heading “Concentration/Dose”.

Page 7-61, line 14: This summarizes data of Table 7-6, however, where are studies summarized which are listed in Table 7-7? They were not described in this section.

Page 7-62, lines 29/30: The statement that iron may play little role in adverse effects of PM is not justified based alone on the results of lung function and lung permeability measurements; certainly there were inflammatory changes in this study by Ghio *et al.* (2001).

Page 7-83, lines 16/18: It is not clear what the dose of 15 µg means, is it inhaled or estimated deposition? Also, what is the particle size of LPS? This would be useful information to give the reader some understanding of how much of the inhaled LPS was deposited in the lower respiratory tract.

Page 7-85, line 13: Add at the end of the line “at higher concentrations or doses”.

Page 7-107, line 6: Replace “these” with “transition”.

Page 7-108, line 4: Rather than giving the rpm for the centrifuge, what were the g-forces?

Line 11 to

Page 7-109, line 29: Possible mechanisms/hypotheses of metal induced effects are described here. When discussing these mechanisms, it needs to be pointed out that the studies were done at high doses and that the mechanisms are not necessarily the same as those being induced at low doses. (This concept of “the dose making the mechanism” was already well addressed earlier in this document).

Page 7-113, line 18: A statement is made here that inhaled particles are trapped in the epithelial lining of the nasal and tracheal airways. I think what is meant is that particles are deposited, or else what study shows that the particles are “trapped”?

Page 7-119, line 28: Newer studies are referred to here which should demonstrate a plausible neurogenic basis for PM inflammation. I am not sure how plausible these studies are, given that large doses were used in an *in vitro* assay only. At this point, this is a hypothesis that requires confirmatory testing.

Page 7-121, line 10: The study by Gilmour *et al.* (1996) was with PM₁₀, not ultrafine TiO₂.

Page 7-124, lines 22-27: it is well known that in addition to particle surface area, chemical composition impacts on the cellular responses to PM. However, I am not sure that the study by Schluter demonstrates this: Was the size of these differently coated silica particles the same for all coatings? Were these fine particles, ultrafine particles? Was the uptake by macrophages the same for the differently coated particles? Not knowing the answers, one has to be careful with the statement as presented here.

Page 7-134, line 6: It should also be pointed out at the end of this paragraph that mortality is only a very crude endpoint in these genetic studies.

Page 7-153: This new section on quantitative comparisons of experimental PM has a very good introductory chapter, although several of the statements in the later sections are somewhat superficial and need to be rephrased, or explained below:

Page 7-166, lines 16-20: An effort is made to compare tissue doses and responses between rats and humans exposed to PM:

Line 17: refers to the surface area dose, please replace the term “tissue dose”.

Line 19: suggests that even healthy humans are notably more susceptible to the inflammatory effects of CAPs than are rats. However, this cannot necessarily be derived from these studies: Rats in this comparison were exposed for 3 days in a row, humans only once, and observed effects are the basis for this conclusion. However, there are data showing (including our own with the highly toxic PTFE particles) that 3 days in a row exposure can cause adaptive responses: Rats in our PTFE studies became less or even unresponsive after 3 days of exposure as opposed to a one-time exposure only. Thus, one has to be very careful comparing different exposure scenarios, *i.e.*, repeated exposures vs. a one-time only exposure; in addition, species differences have to be considered in such adaptive responses, so I think that this comparison and respective conclusion are not valid.

Page 7-168, line 14: The document states: “These *in vitro* studies of human AM may be compared to three available studies that investigated animal AM responses” I don’t think that this can be done so easily, comparing primary human cells to a mouse cell line, how can that be compared? Even when comparing primary human AM to primary mouse AM, it will be difficult: Culture conditions, even using the same culture medium, may be optimal for one or the other species, but not for both, so there are many *caveats* that have to be considered when making such comparisons of *in vitro* studies with cells and cell lines from different species.

Page 7-171, line 5: I suggest to replace “human AM are at least as sensitive” with “human AM may be at least as sensitive”.

I suggest also at the end of this section, line 14, to include a general concluding sentence pointing out that for making comparative statements it is also important 1) to compare the same cell types, include a control particle and evaluate relative

differences of human and rodent primary cells to this control particle; 2) compare the same types of dusts, rather than one with significantly leachable metals *vs.* another devoid of metals. Overall, don't mix PM types and cell types (primary/secondary).

Page 7-185, line 3: Typo, m³.

Page 7-192, lines 8/9: In this study by Driscoll *et al.* (1997), it should be added that the neutrophils in the BAL are the source of ROS, which in turn result in secondary genotoxicity *via* DNA damage; this is quite different from primary genotoxicity. It needs to be also made clear that the results of this study were definitely a high dose effect and that these effects are not seen at low doses.

Page 7-202, lines 1-3: The faster clearance of PM the lower respiratory tract in rats *vs.* humans is most important for long-term exposures and effects; for acute effects differences in deposition between rats and humans rather than clearance differences are more important.

Page 7-204, line 25: The statement in this line suggests that in these studies by Veronesi *et al.* the proton cloud was measured; however, I assume that this is just a mechanism suggested as a likely scenario by the authors.

Page 7-206, lines 23/24: I suggest to again add here that the instilled ROFA involved high doses.

Page 7-211, line 22: As mentioned before, it should be added here that the mutations were due to ROS released from inflammatory cells, resulting in secondary genotoxicity, not primary genotoxicity which is the case for some PAH.

Page 7-216, lines 12/13: It also needs to be noted that adherence of allergen-laden pollen as shown here for DPM has not yet been investigated with other PM; in other studies which were summarized in this criteria document (Steerenberg study) it was shown that DPM was least immunogenic when contrasted with other PM.

Page 7-220, lines 11/12: The MCT model has been repeatedly presented in this criteria document; as pointed out before, this is very likely not a relevant model for human conditions, and I suggest it should not be presented here again as the model for a compromised host. Rather, the difficulty should be pointed out to establish relevant models for human compromised conditions in animals, and that there is clearly a need to search for new and better models to reflect the underlying human pathophysiology.

Page 7-221, lines 22/23: Again, this last sentence points to DPM as one particle that is effective in exacerbating allergic asthma responses; however, so do other particles if they are tested in the same study together with DPM; it would, therefore, be helpful to point out the shortcomings in most of the DPM by studies not having included a comparison particle.

REVIEW OF APPENDIX 7A

Overall, this chapter provides good and thoughtful discussions; it would be desirable to include some concluding comments after individual sections similar to what is done in the summary. Specifically, it would be useful to emphasize more the complexity of dosimetric extrapolations, stressing that this is highly dependent on PM parameters, exposure scenarios, breathing and activity patterns of different species and — not yet achievable by models — expected differences between responses of a compromised host vs. healthy host. The summary does a nice job in this regard, and in between conclusions after individual sections would strengthen this.

Page 3, line 22 and subsequently throughout the chapter and figure legends: I suggest not to use the term “highly insoluble” particles, but rather call them “poorly soluble” particles; I have used this term “highly insoluble particles” myself in earlier publications, but I think the general consensus is that these should more appropriately be called “poorly soluble particles” because there is no particle which is highly insoluble (perhaps iridium is the most insoluble particle so far tested).

Page 4, line 11: The symbols f and V_t need to be explained, *i.e.*, frequency and tidal volume.

Lines 26 – 29: These sentences are a bit confusing: Normalization and uncertainty factors are introduced here together, they seem to blend into each other without distinction, and it needs to be clarified. Also, in line 28, the term “acceptable” human dose is not clear, probably what is meant is “extrapolated” human dose? This continues on line 9 of the next page where the acceptable human dose is defined as 1/3 of the no-effect level for the animals: so the acceptable dose is a no-effect level?

Page 7, line 31: It is stated that the alveolar surface area is not included in the MPPD model, however, the version that has been distributed allows to model alveolar surface area as well (and is also used later in this chapter as a result).

Page 9, line 9: Alveolar rate constants for the rat equivalent to retention halftimes of 100 days, 323 days and 835 days are given here to be used in the retention modeling exercises. These values are from a recent article by Bermudez *et al.*, however, there are numerous earlier studies which show that normal retention halftimes in rats are between 60-80 days, in fact in the article by Bermudez *et al.*, a similar study with TiO_2 by Warheit *et al.* is mentioned which gave retention halftimes of 68 (normal, un-impaired), 110 and 330 days for the same TiO_2 exposures. These values are more in line with the normal rat clearance values observed in earlier studies using radioactive test materials. Use of the lower $T_{1/2}$ may change the predictive modeling results, and it should be indicated here that the modeling exercises are performed only to show principles of extrapolation models and that actual results will vary depending on model inputs, as usual.

For humans there was a three-phase alveolar clearance assumed, which is well demonstrated by earlier studies by Bailey *et al.*, was that also assumed to be the case in rats? Kreyling and Scheuch report a time-dependent clearance rate for the rat as well.

Page 9, line 31: As in my earlier comments, I suggest again that the term “clearance half-time” should be changed to “retention half-time” throughout this section.

Page 10, upper para.: For the human clearance rates in the alveolar region, was there also assumed to be a load dependent retardation as is the case in rats? Although there is no direct evidence in humans for this phenomenon due to the lack of measurements, there is some evidence from coal miners (Stöber; Freedman) that such retardation with increasing lung load does happen. Obviously, such high lung burdens will never be achieved at levels of PM in the ambient air.

Page 11, line 19: Add the term “(mass)” after “ μg ” and the term “(surface area)” after “ μm^2 ”.

Page 14, footnote B of table legend: The reported data for the resuspended PM distributions were done with the use of a cyclone? Give references.

Page 18, lines 1-5: Summary data of my old 1988 retention review are given here; although the general principles of differences among species in terms of particle retention are still the same, I suggest to use newer data, specifically a review by Kreyling and Scheuch (2000, In: Particle-Lung Interactions, Chapter 7: Clearance of particles deposited in the lungs, pgs. 323-376) as the most up-to-date reference. Data in this summary also show that rats as well as other species show a change in the alveolar clearance rate over time, similar to what has been reported by Bailey *et al.* in the 80’s for humans.

Page 22, line 27: Replace “mass” with “dose” in both places.

Page 24, Table 7a-3: Another parameter useful to compare and add here would be the deposited dose per unit surface area of the alveolar region.

Page 26, Table 7a-6: Add a footnote to the slow clearance for humans and add this as b on the table indicating that the alveolar clearance rate is a function of time. Also, stating in the PM size distribution column for humans “exposed to all three atmospheric modes” is not quite correct in case of exposures to CAPs.

Page 28, Table 7a-7: This is an interesting table showing the large variations of EqER and its dependence on selected parameters. For clarification I suggest to add to the title, first line “deposited dose after” before “a 6-hr. exposure”

Page 31, line 2: With respect to surface area of particle aggregates, one would not require very high doses since the aggregated surface area may still be the same as that of singlets; what changes in that case is the deposition fraction and the site of deposition.

Page 31, line 13: The large ranges of EqER values require a concluding comment, rather than just reporting the model values. For example, that this shows how questionable such comparison may be and that there are still a number of uncertainties due to the complexity of the issues.

Page 36, lines 1-6: Under realistic ambient exposures, rats should not enter the overload state, thus, there is no need to consider such scenario. Neither does it for humans as is pointed out here, however, the human model does not include a change of clearance rate with time. That the rat will not reach overload state under realistic exposures is also shown in Figure 7-9, so there really is no need to dwell on the overload situation, but what should be indicated is that in rats, like in humans, the clearance rate changes (becomes slower) with time which is not modeled in these exercises.

Figure 7-9, the labeling on the ordinate is not clear, retained mass as a function of deposited mass?

Page 41, section on “caveats”: It should also be emphasized here that only the dose is considered in these modeling exercises nothing else; other modifiers are: cellular responses; the fact that affected humans are compromised; that there are changes in deposition, retention and response in compromised hosts; that this dosimetry modeling is for healthy rat to healthy human and *vice versa*; for compromised organisms many parameters will change.

In line 11, add at the end of the sentence something about the usefulness of these modeling exercises for study design and avoiding nonsensical rat exposure studies as was discussed on the previous page (*i.e.*, exposure of rats for 6 months to resuspended dust).

Page 43, line 11: It would be helpful to also indicate how much PM material was needed to achieve 500 µg of the extract.

Page 45, line 22: The differences between a subchronic exposure and the highly acute manner of a delivery by instillation is very important and should be emphasized. Obviously, the dose rate is very different, and the dose rate is most important for acute effects. This issue of dose rate should be discussed here, the concept and principle are already addressed in this and the following page.

Page 48, table 7-12: In this table and in the two tables on the next page, the use of the term “equivalent” is not quite correct based on how this is defined in this chapter; it should be rather “predicted”.

Page 50, line 7: The definition of dusts as ‘nuisance’ or ‘inert’ should be avoided rather they should be called “low toxicity dusts”.

Line 21: Reference is made to a discrepancy between the volume hypothesis and surface area hypothesis in overload and other situations: However, this is not really a discrepancy, but it shows our continuing understanding and developing of our understanding over time; with the increasing awareness of ultrafine particles it turned out that the volume concept does no longer hold anymore, but the surface area concept does for poorly soluble particles of low cytotoxicity. That is, surface area appears to be a more appropriate dosimetric to model effects caused by different loads of particles of sizes going down to the ultrafine size range, which case is not well modeled by the volume overload concept.

Page 53, line 24: Reference is made here to the importance of particle size on alveolar macrophage-mediated clearance, justifying using MMADs only between 1 and 4 µm. However,

this covers not the whole problem, aggregated ultrafine particles can also have a MMAD of 1 μm , yet still they elicit responses due to their unchanged large surface area rather than their volume (see studies with instilled and inhaled aggregated ultrafine vs. fine TiO_2).

Page 55, lines 2 and 3: The statement that high concentrations given to rats may also better simulate high deposition at “hotspots”, or in active portions, of the diseased human lungs does not necessarily hold; there are no data to suggest this; moreover, if higher concentrations are used for rats, this will create even greater hotspots in that species, not just the normal hotspots seen anyway.

Page 58, lines 19/20: Again, it is suggested here that there may be occasions where some extent of overload could be needed to mimic certain human conditions: One has to be careful with this suggestion: Which decreased pulmonary defenses in humans should be modeled by a particle overloaded rat? If there is a specific case state it here or else delete this sentence.

Page 59, Conclusions:

- - First bulletpoint, I suggest to add in line 2 “in certain conditions” after “would be justified”.
- - Second bulletpoint, line 3, this sentence needs to be turned around and read like this: Given that rats clear PM much faster than humans, the MPPD model results show that much higher Also, in the last line of this bulletpoint – replace “highly insoluble” with “poorly soluble” particles.
- - Bulletpoint 3, line 4: Resuspended PM does contain the smaller particles, but they are aggregated onto the larger ones.
- - Bulletpoint 4, line 5, 4th and 3rd lines from bottom: Insert the word “healthy” before “rats clear PM.....” and before “humans”.

Dr. Robert D. Rowe

Memorandum

To: Fred Butterfield
From: Bob Rowe, Stratus Consulting Inc.
Date: 7/9/2004
Subject: Review comments on PM CD Chapter 9, June 2004 Draft

Chapter is much improved and close to closure, subject to clean-up. Detailed comments follow.

Section 9.3.1 Visibility

The text places emphasis on the term “public values,” which conjures up a focus on monetary valuation (see page 9-102 line 25, page 9-105 lines 15-23 and page 9-106 line 3). A broader phrase, such as “public perceptions, attitudes, and values,” may be preferred to blend the relevant information and messages from the newer studies (e.g., the cited Denver/Phoenix studies that are about perceptions and attitudes about what constitutes adverse conditions) and the older economic studies (where monetary valuation is emphasized in as an indicator of adversity).

The CD does little in Chapter 4 to meaningfully combine information from the old studies and the newer studies identified to address relevant questions such as “how much or what characteristics of impairment are adverse?” and “how adverse is it?”. This limitation carries on in Chapter 9 on page 105. On lines 15 through 23 the newer studies are set aside as something different than the older studies, but being only two newer studies the text identifies there may be too few to base policy on. However, both sets of studies suggest, through different metrics (with different measurement issues), that current levels of anthropogenic caused visibility impairment are viewed as adverse by a share of, if not a majority of, the public. In the two newer studies, adversity ratings clearly indicate that levels that are experienced routinely in the two study cities and elsewhere are adverse. In the economic valuation studies the estimated dollar values can be considered an indicator that current levels of impairment are adverse, even allowing for uncertainty in the precise dollar values assigned.

Given the Criteria Document’s focus on the limited new literature, minor wording improvements may be sufficient for closure. However, for the Staff Paper EPA should consider more serious efforts to see if and how all the literature can be used to address key questions relevant to selecting a secondary standards.

Page 9-102 Line 24. For consistency, consider replacing “affects” with “impairs.”

Section 9.3.2: Vegetation and Ecosystems.

This section is better than prior iterations; particularly the introduction and summary, and is much closer to acceptance. The section can use some tightening and clean-up.

- In places the text tends to provide discussion that may be longer than necessary for the synthesis of key points for evaluating potential standards. Page 9-108 seems to retreat to laying groundwork rather than staying focused on key implications for impacts to individuals, populations and the ecosystem. Page 9-110 lines 3-7 are unnecessary.
- While many of the key points from Chapter 4 relevant to the state of the science and its implications to standard setting are carried forward here, I wondered about the omission of others, including:
 - Experimental applications of PM constituents to foliage typically elicit little response at the more common ambient concentrations (June 2003 draft page 4-60 line 24);
 - Although forest ecosystems other than the high-level spruce-fir forests are not currently manifesting symptoms of injury directly attributable to acid deposition, less sensitive forests throughout the United States are experiencing gradual losses of base cation nutrients, which in many cases is expected to reduce the quality of forest nutrition over the long term (page 4-115). Acidic deposition is having a significant affect on nutrient cycling in most of the forest ecosystems studied in the IFS project (page 4-136).
- Page 9-106, line 24. Sources include mining emissions beyond just iron and lead smelting.
- Page 9-106, lines 25-27 is it correct to say “these effects tend to be limited in scope” as the reason for dismissal here of these situations or is it that these cases are generally addressed through regulatory strategies other than the PM SNAAQs.
- Page 9-114, line 27. The line is confusing “nitrogen or acidic deposition its role...”

Section 9.3.3 Climate

- Page 9-116, line 26. Although “degradation” is fine, “impairment” may be preferred for consistency with the visibility section terminology.

Section 9.3.4 Material

- Page 9-119, second to last sentence can be a bit broader. “Available data indicates that airborne particles can result in increases in the frequency of cleaning, maintenance, or replacement of exposed surfaces and materials, as well as reduced usefulness and enjoyment of injured materials (as is the case with stone monuments or dirty buildings).
- Page 9-110, last sentence. The focus on perception and perception thresholds seems limiting. Attempts have been made to both address the perception threshold of soiling and the welfare consequences. Also, while there has been little new on traditional soiling costs, some new work on public values with respect to cultural monuments/buildings has occurred and continues to indicate that ongoing degradation of cultural sites is viewed by the public as adverse. (S. Navrud and R.C. Ready (eds.) 2002. *Valuing Cultural Resources*. Edward Elgar, Cheltenham, UK, ISBN I-84064-079-0.)

Dr. Jonathan M. Samet

Jonathan Samet, M.D., M.S.

Professor and Chairman

**Jacob I and Irene B. Fabrikant Professor in Health, Risk, and Society
Johns Hopkins Bloomberg School of Public Health**

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

General:

This revised chapter continues to improve; of course, given its length and scope, additional points for revision can always be identified. However, I find that the chapter has been improved sufficiently to warrant its being approved as final, with some minor modifications. The chapter appropriately sets out how the evidence was gathered and evaluated, and provides clear summaries of the relevant data. Consideration might be given to incorporating some of the material in section 8.5 into Chapter 9, as this material reflects an integration of the epidemiological findings with other information, largely related to causal inference. I note that the chapter begins with a description of the “Hill” criteria for causality, but these criteria are in fact not uniformly applied, either in this chapter or in Chapter 9.

The initial text, offering a primer in epidemiology, has sharpened. I find some of its statements too sweeping and have highlighted these below in my specific comments. The chapter offers the view that “correct” models can never be identified and that there is always a potential for residual confounding. This proposition is hardly unique to studies of particulate matter and health, and has not been a barrier to the use of observational evidence in other contexts. Confounding is of greater concern when effect sizes are small, as in this case. However, the sweeping generalizations need to be toned down.

Specific:

Page 8-10, Lines 3-15: this paragraph is not well written and might benefit from inclusion of a figure.

Page 8-12, Lines 6-7: this statement is far too general. What is meant by “none of them being completely satisfactory”?

Page 8-13, Lines 8-17: most important, but not mentioned, is the sensitivity of findings to the details of model specification. The finding of an association that is robust should be taken as evidence that substantial confounding “or model misspecification” is not strongly affecting the effect estimate.

Page 8-327, Lines 27-31: why do the authors of the Criteria Document look for “consensus”? Again, sensitivity of findings to alternative specifications needs emphasis.

Page 8-327, Lines 39-40: again, a similar sweeping statement.

Chapter Nine: Integrative Synthesis

General

The Environmental Protection Agency is deserving of congratulations for taking a first step towards developing a satisfactory “integrative synthesis” of the Criteria Document. In comparison with the prior draft, the present chapter is more than simply a culling of the summaries of the individual chapters. There is an attempt to draw the evidence together around a set of key uncertainties in any further evolution of the NAAQS. Nonetheless, I have some major concerns with regard to Chapter 9, which should still undergo substantial revision:

- The chapter remains too long, comprising 119 pages of text, with many additional pages of tables and figures. Too much detail is included, and I suggest a careful editing in this regard. For example, some text needlessly repeats the results of individual studies. I suggest not giving details of any individual study, unless the evidence is regarded as pivotal.
- My greatest concern lies in the approach to developing the “Summary and Conclusions” sections. These are the critical elements of the synthesis, and should clearly specify the additional knowledge gained since the 1996 Criteria Document, the starting point for this review. Each section related to the major questions carefully sets out where the knowledge stood in the last document. However, statements as to the extent of knowledge gains are variable in length and in the approach taken to characterizing the gain in evidence.

Perhaps, these sections are generally weak because clear rules were never set out for evidence interpretation. Additionally, there is a disturbing difference in approach as the section beginning on page 9-80 considers the “coherence of evidence” at length, while similar sections are not provided for the other major issues. This section, extending from pages 9-80 through 9-84, offers a potential model for how other sections might systematically evaluate evidence.

However, the section suffers from an overuse and excessive reliance on the term “coherence” which is variably used. I caution EPA against developing another approach to evidence evaluation, (i.e., are based on “coherence”) which may differ from approaches taken in other Agency reviews and which diverges from general practice in public health. Models for evidence evaluation are available from reports of the Surgeon General and the National Research Council, for example.

- Additionally, the material on health effects might benefit from a several page summary, which is truly “integrative” across the full body of the chapter. The degree of certainty overall might be addressed in such a section.

Specific comments:

Page 9-1, Lines 27-29: Research recommendations might be usefully placed in a single section. At present, I found them scattered somewhat haphazardly throughout the text.

Page 9-6, Lines 11-14: There is inherent inevitability in the choice of PM metrics used for health research; EPA has shaped research in its choices and by the size fractions monitored.

Page 9-17, Lines 12-21: These statements are sweeping and far too general. I caution against such broad calls for research. Additionally, the authors should decide where research recommendations might best be placed in the text, and certainly they should be separately identified as such.

Page 9-19, Line 17: What does “highly multifactorial” mean?

Page 9-19, Line 23: The statement “frequently being statistically significant or nearly so” should be removed.

Page 9-20, Lines 4-8: While the multi-city studies have the mentioned strengths, their results receive little emphasis in this section.

Page 9-31, Line 9-32, Lines 30-2: What evidence can be cited to support the concluding phrase of the sentence “in conjunction with covarying gaseous pollutants.” Much of the cited evidence weighs against effect modification and changes in effect estimates with inclusion of gaseous pollutants in models may represent the contribution of the gaseous pollutants to secondary particles.

Page 9-33, Line 28: Would not a greater proportion of susceptible people imply a higher overall mortality rate?

Page 9-35, Lines 21-23: I am not sure I agree with this comment concerning selection of single-day lags.

Page 9-36, Lines 9-14: I am concerned that the authors are overinterpreting the study of Mar et al., and perhaps giving undue weight to possible chance variation.

Page 9-39, Lines 18-27: This section is particularly brief and weak and needs substantial expansion.

Page 9-41, Line 28: Perhaps a missing phrase?

Page 9-42, Lines 9-11-13: This sentence is too ambiguous; what is meant by “at least under some circumstances”?

Page 9-45, Lines 3-12: This material is too vague and needs sharpening.

Page 9-49, Lines 26-27: What is meant by “the most applicable to risk assessment”?

Page 9-52, Lines 11-15: Another unclear sentence.

Page 9-57, Lines 20-25: Research recommendations again offered haphazardly. I also think that the recommendation is far too general to be useful, and the comment concerning mixtures offers far too simplistic a suggestion concerning a difficult problem.

Page 9-70, Lines 19-26: Quite confusing discussion and use of the term “causality” in a fashion that I cannot readily interpret.

Page 9-80, 9-85: I have previously commented on the use of the term “coherence”. In this section, the phrase is used relatively often, appearing to refer in some instances to consistency of epidemiological findings and in others to parallel and complementary findings in different lines of investigation, e.g. epidemiology and toxicology. I would urge that the authors not “abuse” the concept of coherence, which has proved too convenient in these pages. As I noted in my general comments, the other major issues do not have a similar discussion, which might be helpful.

Page 9-101, 9-102: This section is also weak. For example, Line 22, Page 9-101 comments that “the public health impact of exposures to ambient PM can be quite large”; this is far too general a description of public health impact.

Dr. Sverre Vedal

Critique of 2004 revisions of draft PM Criteria Document (chapters 8 & 9)

Sverre Vedal

July 20, 2004

Chapter 8:

1. General.

This revised draft has dealt with nearly all of the issues I had raised about the previous version, and nearly always successfully. Disagreements that I have with the CD at this point are largely due to differences in interpretation of the evidence rather than concerns about fair representation of the findings or about factual errors. Rather than detail the many points where the CD has improved, I will touch largely on those where the authors elected either to leave the CD unchanged, or where the changes are not adequate.

2. Cohort studies.

The VA cohort study is now treated more fairly than before.

On a seemingly small issue regarding the description of the Hoek report from the Netherlands on the association between residence in proximity to large roadways and mortality, I still maintain that the unadjusted effect estimate for black smoke (1.34) reported here in the summary of that report (p.125, line 9) should not be reported. This is similar to reporting Six Cities and ACS cohort findings unadjusted for individual risk factors. It was the ability to perform this type of adjustment for individual-level risk factors that set these two studies apart from the previous generation of cross-sectional ecologic studies. This unadjusted estimate in the Hoek study 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. While these effects do not negate findings from the other cohort studies, they do nevertheless add fuel to an argument that findings from the spectrum of cohort studies are not necessarily in agreement (consistent).

3. Natural experiments.

There is again reference to both respiratory hospitalizations and mortality (p.9-126, L8) in the description of the Utah Valley steel mill closure. The formal study that directly used the steel mill closure in the design only involved respiratory hospitalizations. Mortality was only analyzed using a traditional time series design (Pope 1992). In that paper it was stated that average deaths per day were 3.2% higher when the steel mill was open than when it was closed. The baseline daily mortality was 2.7 deaths/day, which translates to less than a 0.1 death per day increase with the steel mill open. The absence of statistical power here explains why this “finding” was never emphasized, quite correctly, except in this CD. The continued reference to mortality here in the CD is not justifiable, at least without appropriate qualifiers.

A small issue regarding the “natural” experiments in Dublin and Hong Kong: it is claimed that these are not useful for quantitative risk assessment (p.130, L1). On the contrary, given that one can be more confident about control of confounding in these studies, I would maintain that they are preferred over either the cohort or time series studies for this purpose. It seems that the only rationale for not including considering them for this purpose is that the time

course of effects is not clearly the same as that in either the cohort or time series studies. This is a weak rationale.

4. Co-pollutants.

The discussion on gaseous pollutant variables as possibly acting as surrogate measures of some features of PM composition continues to be illuminating. However, in my opinion there is too much made of this point (pp. 9.229-231, and elsewhere) since it remains highly speculative. As I have noted before, a more cogent argument can be made that daily variations in the concentrations of these pollutants serve as measures of unmeasured features of meteorology, given that meteorology is the primary determinant of daily concentration changes and, arguably, a more plausible cause of these health effects than the small daily concentration changes in either PM or the gaseous pollutants.

Specific &/or editorial comments:

8-5, L21, etc.: In the description of study designs, although panel studies are now no longer linked with cohort studies (an improvement), they have now unfortunately been dropped altogether. I propose including one group of studies under the “longitudinal” rubric to include: cohort (semi-ecologic), panel, intervention, time-series (and its variant, the case-crossover study). The “non-longitudinal” study types are ecologic, cross-sectional and case-control.

8-48, L2: “that” = “than”

8-68, L6-7 & 8-77, L12: 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.

8-145, L9-11: This work was referenced in press in the last version, and is now referenced from 2004. I protest. Many equally important studies have not been referenced in the CD because of the date cut-off. The same should apply to this study.

8-153, Figure 8-10 & 8-187, Figure 8-12: Again, what is the basis for selecting the specific studies included in these plots? This is relevant because they are used to generate a range of effect estimates for this outcome.

8-262, L8-10: Again, 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.

Chapter 9:

Overall, I found the organization around the 5 questions to be helpful. This was more of an integrative synthesis, as intended, although I have criticisms.

Question 1. *How does newly available information continue to support consideration of fine and coarse particles as separate subclasses of PM?*

I found this discussion credible and useful.

Question 2. *How does newly available information inform our judgments about the strengths and limitations of epidemiologic evidence for health effects related to ambient fine and coarse thoracic PM, acting alone and/or in combination with other pollutants?*

My comments here are quite specific, and often reiterate objections that I have raised in earlier critiques of chapters 8 and 9.

1. Statistical model specification.

It should be noted that most of the re-analyses included in the HEI report did not report findings using “alternative modeling strategies” (p.9-3, L3-6). In fact, the few that took other approaches found that impacts on effect estimates could be large and often changed the qualitative conclusions, as opposed to the conclusion presented here.

2. Co-pollutants.

See my comments on chapter 8 on the topic of gaseous pollutants as PM surrogates. These are equally applicable to similar statements here (p. 9-30, L27-). Regarding the relatively strong effect of SO₂ in the ACS cohort study, to conclude that it is difficult to interpret because SO₂ is a precursor of sulfate (p.9-31, L20-21) is too dismissive and not very thoughtful.

3. Heterogeneity of effects.

While chapter 8 of the CD qualifies the lack of statistical evidence for heterogeneity of effects in NMMAPS by noting the limited statistical power of this test in this setting, no qualification of this conclusion is included here (p.9-33, L14-15).

4. Consistency of findings.

The use of “consistency” (section 9.2.2.2.3, p. 9-33 to 35) to describe estimates of effect from the entire body of studies (particularly the large body of time series studies) has, to my mind, become nearly meaningless (note that my take on the use of “coherence” below [question #3] is similar). This descriptor is repeated so often that it is now accepted without any thoughtful assessment as to what it really means, or at least what it should mean. The way it tends to be used in this setting is that if a study reports an effect at any lag, and for some model specification, it is regarded as a “positive” study, and hence consistent with all others in which an effect is reported. It is very difficult for a study to be “negative”, given all of the associations that are inspected in these studies, so consistency, by this definition, is almost guaranteed. Statement of specific hypotheses at the outset of a study would help to partially circumvent this unfortunate trend, but hypotheses are typically general enough that it is difficult for them to be falsified.

5. Lagged effects.

Justification for the use of “best” lag is presented here again (p. 9-35). Given that I have tried to argue against this, the authors of the CD must disagree with me and seem committed to coming up with a justification for using “best” lag. I repeat again, this selection process guarantees bias.

I am unclear how the pattern of persistence of pollution in a city (p. 9-35, L 26-31 and p. 9-37, L6) affects the lag structure. This may influence how one specifies a pollutant measure in a city (e.g., number of days to average), but the link with lags is unclear.

6. Found (quasi-experimental) studies.

It is again claimed that the Utah Valley steel mill closure study reported effects on mortality as well as on respiratory hospitalizations (p. 9-38, L 31). See my Chapter 8 comments on “Natural experiments” above.

Minor/editorial:

9-19, L2: “know” should be “known”

Table 9-6 (p.9-22). Note under PM_{2.5}, “dysrhythmias” are listed under “Resp Diseases” and claim reference #12, which is the Seattle study of asthma.

9-23, L14 (first line): “PM_{2.5}” should be “PM_{10-2.5}”

9-33, L28: Why would a lower mortality rate suggest that “more susceptible people” would be present? I would have thought that a lower mortality rate indicated a healthier population (i.e., less susceptible).

Question 3. *How does newly available information inform assessment of biological plausibility and coherence of health effects attributed to ambient fine and coarse thoracic PM and/or their components?*

In general, this part provides an evenhanded presentation of findings. Identification of inconsistencies among studies was refreshing and useful.

The section summarizing the epidemiological findings (section 9.2.3.2.1, pp.9-41 to 44) is unnecessary. Further, the attempt to identify a role for regional sulfate in this section based on the studies that employ factor analysis (p.9-44, L3, etc.) to identify sources (i.e., indirectly) is poorly justified, especially in light of studies that employ a direct measure of sulfate concentration. Further yet in this section, what does lag have to do with confounding (p.9-44, L13-15)? In short, this entire section is unnecessary and does a poor job of fairly reflecting the epidemiology.

Three general categories of effects (cardiovascular, respiratory and mutagenic/genotoxic) are reviewed (pp.9-54 to 59). Are systemic inflammatory effects intended to be included under cardiovascular heading? In addition, it would seem that vasoconstrictive effects (Brook human exposure study) should also be included.

A great deal of space is devoted to a discussion of coherence (p.9-80, etc.). Like “consistency”, “coherence” has been repeated so often it is now accepted as a given. In this setting, coherence is claimed when effects on two or more outcomes have been observed in a city. Hence, reference is made (pp.9-81 to 82) to figures 8-24 to 8-28 in chapter 8 (pp.8-263 to 267) for Los Angeles, Chicago, Detroit, Pittsburgh and Seattle. However, no quantitative assessment of coherence wherein the correlation between effect estimates is analyzed for more than one outcome across cities has yet been published (although NMMAPS IV concerns itself with this issue). Further, coherence is moot in the absence of consistency, yet we seemingly have rushed forward and claimed coherence when consistency remains at issue.

Once again there is reference to the Utah Valley steel mill closure study (p.9-83, L4-12) and mortality effects. Again, see my Chapter 8 comments on “Natural experiments” above.

Question 4. *How does newly available information inform our understanding of subpopulations potentially susceptible to PM-related health effects?*

It is unclear whether it is being argued that the elderly are more susceptible by virtue of chronic diseases being more prevalent in the elderly, or whether higher age alone increases susceptibility.

Regarding gender effects, there was no mention of the important gender effect in the cohort mortality studies: in the ACS study, the lung cancer effect was only seen in males, and in AHSMOG, the mortality effect was only apparent in males.

Question 5. . *What does the newly available information imply with regard to potential public health impacts of human exposures to ambient PM in the United States?*

Much of section 9.2.5.2.2 is a general review of observational findings and is unnecessary; the points relating to the size of the susceptible pool and on the size of effect estimates are valuable, however.

Mr. Ronald H. White

Comments of Ronald White, M.S.T. on EPA Criteria Document for Particulate Matter, Chapter 8: Epidemiology of Human Health Effects Associated With Ambient Particulate Matter (June 2004)

The sixth iteration of this chapter of the PM Criteria Document provides further refinement of the PM epidemiologic literature review that was already quite comprehensive in the previous version, and addresses the major concerns raised by the CASAC review of the previous draft document as well as many of the issues raised by other credible scientific reviewers.

Issues related to overinterpretation in the previous draft of this chapter regarding the biological significance of cardiovascular endpoints such as changes in heart rate and heart rate variability have been appropriately revised, as have the more speculative statements regarding the possible mechanisms for cardiovascular-related mortality outcomes.

The revised chapter provides a more balanced discussion of several of the studies finding mixed or negative results (e.g. Lipfert et al. 2000 VA cohort study; Abbey et al. 1999, Beeson et al 1998 ASHMOG studies), as well as expanding the discussion of the cautions and limitations in interpreting the results of many of the time series and cohort studies included in the chapter. Key intervention studies (e.g. Clancy et al. 2002; Hedley et al. 2002) that CASAC suggested for inclusion in the chapter have been added and, in general, appropriately interpreted. The discussion of the results in Hong Kong from the Hedley et al. study would, however, benefit from an improved discussion of the potential role of reductions in sulfur dioxide on mortality and the implications of this finding for other studies where a mortality effect of SO₂ was found.

The revised chapter also expands and improves the discussion of the potential methodological uncertainties related to measurement error and model specification in evaluating the epidemiologic results.

In conclusion, this revised draft of the PM Criteria Document chapter on the epidemiological evidence of the health effects of particulate matter improves on an already encyclopedic and generally well written review of the scientific literature published since 1996 on this topic. The authors have adequately addressed the vast majority of CASAC's criticisms and suggestions for improvements of the previous draft document. As such, I find the chapter sufficient for meeting the Clean Air Act statutory requirement to "accurately reflect the latest scientific knowledge" and recommend closure for this chapter of the document.

Comments of Ronald White, M.S.T.
PM Criteria Document Chapter 9: Integrative Synthesis (June 2004)

General Comments

This revised draft of the PM Criteria Document Chapter 9: Integrative Synthesis represents a substantial advancement over the previous drafts of this chapter, and provides a much improved integration of the key material from the previous chapters of the Criteria Document. The organization of the material around the five key questions provides an appropriate structure for an integration of the information contained in the previous chapters of the CD. In general, the discussion of the scientific information from the previous CD chapters provides a reasonable balance of indicating the overall results of the scientific information while acknowledging the limitations of the available information.

However, some sections of the chapter (e.g. section 9.2.3.2.3.) still contain a substantial amount of detail related to specific study results that could benefit from judicious editing to enhance the readability of the chapter. The amount of detailed material tends to obscure the key points being made in several of the sections to address the related question. This could be accomplished by reducing the number of specific study citations (as is the case in some sections), eliminating or moving tables summarizing study results to an appendix, as well as referring the reader to material contained in the earlier chapters of the Criteria Document where appropriate (as is done in section 9.2.3.2.6).

There is extensive reference to “consistency” and “coherence” of study results throughout this chapter. A clearer definition of what is meant by these terms (and how they differ) in the context of this chapter would be a useful addition to the chapter introductory material that discusses how EPA evaluates scientific evidence (pg. 9-3, lines 8-18).

In conclusion, while this draft of Chapter 9: Integrative Synthesis requires further editing to pare down the amount of material and improve the consistency of the tone and amount of specific study detail in the different topics covered, it represents a reasonably well done and comprehensive synthesis of the key new scientific findings contained in the previous chapters of the PM Criteria Document.

Specific Comments

Pg. 9-2, line 10: Emerging evidence from human clinical PM exposure studies related to cardiovascular endpoints should be specifically noted here as well in the context of evaluating the epidemiological evidence. This point is also appropriate for pg. 9-3, line 3.

Pg. 9-19, line 23: “Nearly” statistically significant is a vague term, and doesn’t add to the argument for the strength of the epidemiologic evidence. Statistical significance is only one, albeit important, measure of the strength of epidemiologic study results.

Pg. 9-23, line 12: Given the much larger prevalence of cardiovascular deaths in comparison to respiratory deaths, the reduction in precision of the risk estimates for the later in comparison to the former is not unexpected and should be explained in that context.

Pg. 9-23, line 14: This should read PM_{10-2.5}, not PM_{2.5}.

Pg. 9-45, lines 6-9: The implications of the sub-daily time lags from the results of the cardiovascular studies discussed in this section for the PM NAAQS averaging time and protection from CV health outcomes deserves more discussion.

Pg. 9-49, line 20: A brief (1-2 sentence) summary of the conclusions of the EPA dosimetric modeling would be useful here.

Pg. 9-89, lines 15-16: The emerging (though limited) evidence of the effects of PM on neonatal mortality and birth outcomes should be mentioned here as well, and given the birth outcomes data pregnant women also identified as a potentially susceptible population.

Pg. 9-92, lines 16-18: The ASHMOG and ACS studies (Beeson et al., 1998; Abbey et al, 1999; Pope et al. 2002) indicate a lung cancer mortality association with long-term PM₁₀ exposure for males only, and should be noted here.

Pg. 9-94 line 29 – Pg. 9-95, line 2: Given the limitations of the exposure assessment methodology in the Hoek et al. study, substitute another example from the traffic proximity health effects literature.

Pg. 9-95, lines 5-14: Section 9.2.4.3 summarizing the discussion of susceptible subpopulations should be expanded to more directly emphasize the previous discussion of enhanced susceptibility due to age (elderly and children) and disease status. There should be discussion here on the identification of potentially susceptible populations that have emerged or for which data has expanded since the 1996 CD (e.g. diabetics, neonates).

Dr. Warren H. White

Chapter 9 comments by Warren White, 7/29/04

Conceptualization of PM

This chapter is a thoughtful and well-developed introduction to the subject of the CD. There is one area in which it leaves me a bit unsatisfied, though, and that is its easy acceptance of aerodynamic size as the “fundamental” discriminator between particle types, overriding other measurable properties such as chemical composition, water uptake, optical indices, or size distribution moments. This approach accurately reflects current consensus in the aerosol community, but I want to keep the door open to alternatives in future reviews.

We would like our PM categories to “carve nature at its joints,” and we all recognize that the atmospheric aerosol includes fundamentally different particle types. My point is that these fundamental particle types fit comfortably into a variety of different taxonomic schemes, and that privileging one particular scheme as normative can inadvertently constrain our subsequent thinking about atmospheric and biological mechanisms and relationships.

A former Chair of CASAC wrote a book some years ago with the title “Smoke, Dust, and Haze” (Friedlander, 1977), and we can do worse than to take these labels as the beginning of a PM taxonomy.

* At the upper end of the particle-size spectrum are the primary emissions from mechanical processes operating at ordinary temperatures: “dusts” and, as the API public commenter reminded us, “sprays.” “**Dusts and sprays**” correspond fairly exactly to what EPA means by the “coarse mode.”

* At the small end of the size spectrum are the primary particles that nucleate in the effluents of high-temperature combustion processes. These “**combustion nuclei**” are pretty well what health scientists have in mind when they speak of “ultra-fines”. They are a part, but not the whole, of “smoke”.

* In the middle is the secondary material that accumulates in 0.2-2 μm particles through nucleation or condensation from the gas phase, evaporation of aqueous droplets, and coagulation of nuclei with other particles. This hygroscopic “**haze**” formed in the atmosphere is the essential component of the “accumulation mode”, and in many areas contributes most of the mass in the “fine mode”.

The components “dusts and sprays,” “combustion nuclei,” and “haze” map fairly neatly into distinct ranges of particle size, as just noted, but they map equally well into other observable distinctions.

Chemistry: Combustion nuclei are enriched in heavy metals and elemental carbon soot; haze is dominated by ammonium, nitrate, sulfate, and organic material; dusts and sprays are distinguished by identifying species such as silicates and salts.

Water uptake: Dusts and sprays are of course respectively insoluble and soluble. Combustion nuclei are typically insoluble. Haze aerosols are not just soluble, but actively hygroscopic.

Optics: Combustion nuclei are the main absorbers of light, and this absorption can be monitored in real time. The haze species and sprays are essentially non-absorbing in the visible, and most soil dusts absorb only weakly.

Integral moments: Nuclei usually dominate the number concentration, haze usually dominates the surface area and light-scattering cross-section concentrations, and dusts and sprays supply much of the mass concentration when they are significant components. Number concentrations and light-scattering coefficients are particularly suited to *in-situ* and real-time monitoring.

Is a particle's aerodynamic diameter in ambient air somehow more "fundamental" than its other properties? No – once a particle is inspired into the presumably saturated air of the thorax, even its aerodynamic behavior is determined as much by its chemical composition (whether hygroscopic or hydrophobic) as by its diameter in dry ambient air. Even after overlooking this real complication, dosimetric modeling finds "no sharp cut points that clearly distinguish between particle size ranges with relatively high versus relatively low fractional deposition rates." (9-15/9-11). Moreover the separate biological effects of insoluble nuclei – e.g., demands on clearance mechanisms – presumably don't simply vanish when are engulfed within an accumulation-mode droplet, even though their inclusion has negligible impact on that droplet's diameter.

I am not arguing that real ambient aerosols are more complex than the current picture of a coarse mode and a fine mode, or the emerging refinement of coarse mode, accumulation mode, and ultra-fines. I am *not* trying to make the point that "everything is complicated." I am only trying to say that there are *other* useful descriptive frameworks that are just as simple as particle size. As an example, one could define smoke, dust, and haze in terms of black carbon, silicon, and sulfur as the respective indicators, all of them measured by light absorption and XRF on the same Teflon PM₁₀ filter. There would then be no need for the CD's subtle expositions of the distinctions between fine particles, the fine mode, and PM_{2.5}, or discussions of 1 μm vs. 2.5 μm as cut-points. There would, of course, be a different set of angels-on-pinheads debates.

I don't expect the foregoing to convince anyone that EPA should now switch from particle size to chemical composition or some other basis for its PM standards, and I'm not sure I would want it to do so. All I'm really seeking is a clear and continuing acknowledgment, in this CD and in subsequent documents, that particle size is one of several indicators that are useful in distinguishing particles from different sources having different effects, and not uniquely *the* determinant of particle properties. I suppose we can't put new words into Ken Whitby's mouth at 9-4/25 (I wish he had said "The distinction between 'fine particles' and 'coarse particles' is an indicator of fundamental differences" there), but perhaps at least 9-15/23-25 could be changed to read:

The distinction articulated in the last review, between fine and coarse ambient particles as indicators of fundamentally different sources and composition, formation mechanisms, transport, and fate, remains generally unchanged.

The coarse particle mode

The following three statements are potentially misleading, as they may be read to suggest that the fine tail contributes an unusually large fraction of coarse-mode PM in dry dusty areas and dust storms.

9-5/19 ...in dry dusty areas, resuspended coarse-mode particles may extend down to about 1 μm ; ...

9-7/1 ...in dry dusty areas, coarse PM (e.g., resuspended soil) may have a tail reaching to 1 μm or below.

9-10 table bottom. [coarse travel distance is]

<1 to 10s of km, (100s to 1000s in dust storms)

Fine coarse-mode PM is indeed elevated in dry dusty areas and dust storms, but coarse and giant particles are proportionately even more elevated. The coarse and giant particles are preferentially attenuated as they move away from these sources, so the fine tail is actually a larger fraction of the coarse mode away from dry dusty areas, and the characteristic lifetime of the coarse mode in dust storms is shorter than it is at similar altitudes under fair conditions. The fine tail of the coarse mode is always there, in other words. The point you mean to make, I think, is that it is most important as a component of PM_{2.5} when the coarse mode dominates the fine mode – this is the significance of dry dusty conditions and dust storms.

Visibility

Rich Poirot and I have been pushing throughout this review cycle for a clearer acknowledgment of PM_{2.5}'s dominant role, as modulated by relative humidity, in determining visibility impacts. The very first substantive statement here aims explicitly to obscure this point:

9-103/6-8: More specifically, the efficiency ... depends on not just the mass of fine particles, but also on ... [emphases added]

As a more positive substitute that says the same thing, I suggest substituting the following

9-103/6-9: More specifically, light scattering and absorption by particles of given composition and size distribution are strictly proportional to their mass concentration in the air. These optical interactions, by which airborne particles degrade visibility, are well characterized in terms of a light extinction ...

On another point, I disagree with the claim that

9-104/12: Our understanding of how ambient PM affects visibility has historically focused on visibility impairment in rural areas, particularly in national parks and wilderness areas ...

and

9-104/24: ... historically the relationship between ambient PM and visibility has been less well studied in such [urban] areas.

I would argue that the majority of our current understanding and theory – for fine particles in general, and not just visibility – actually derives historically from urban studies, particularly in early-1970's Los Angeles (the concepts of bi-modal size distribution and extinction budget, estimation of species' extinction efficiencies by multiple regression, accounting conventions such as the value 1.4 for organic compound/carbon mass ratio) and in early-1980's Detroit (measurement of particle-bound water contribution, sophisticated aerosol optics modeling (Chris Sloane), accurate characterization of absorption).

Dr. George T. Wolff

Comments on Chapters 7, 8 and 9 of the June 2004 Criteria Document for Particulate Matter

George T. Wolff
(7/13/04)

Chapter 8

1. p 8-2, lines 30-31 to p. 8-3, lines 1-2 – It is stated that papers published after April, 2002 will be included if they provide “particularly important information helpful in addressing key scientific issues.” On p. 8-3, line 14, “model specification” is listed as one of the important issues that this chapter addresses. A paper, brought to the Agency’s attention during our February 2004 teleconference and in written comments, that appears to be central to this issue is not discussed. The paper by Koop and Tole (J. Envir. Econ & Mgt., 47:30-54, 2004) and several other references cited within question whether time-series studies are a valid way to study air pollution-mortality relationship. Since almost the entire chapter and its conclusions are based on time-series studies, these papers cannot be ignored.
2. p. 8-20, line 14 – “interpreted with caution” is misleading. Any results from uncorrected GAM studies should be ignored.
3. p. 8-22, lines 19-20 – I don’t see how this follows from the discussion on pages 8-19 to 8-20.
4. p 8-22, lines 20 – 22 – How can this be stated in light of the “interpreted with caution” statement on p. 8-20.
5. p 8-35, line 4 – “weakly associated” – This is very misleading. If you examine figures 12 and 14-16 in the revised NMMAPS, you will see that there is one lag for each of the gases that show a significant correlation and an effect equal to or greater than PM.
6. p. 8-70 to 8-74 – Somewhere in this section, it should be pointed out that Pb was used as a tracer for vehicle exhaust in these studies that utilized relatively old air quality data. Presently, and for the last 10 years or so, we can no longer use lead as a tracer of vehicles, because highway vehicles no longer burn leaded gasoline. In those intervening years, vehicle PM emissions have declined significantly as the composition has changed as well. Consequently any inferences drawn for these studies, may have no applicability to the situation today.
7. p. 8-73, line 13 – After “vehicle” insert “/road dust.”

8. p. 8-80, line 5 – The “more than 80 new time series studies” makes a great sound bite, but will be used out of context without the accompanying caveats. I suggest you delete it and just talk about the non-contaminated studies.
9. p. 8-81, lines 12-18 – If you look at figures 12 and 14-16 in the NMMAPS reanalysis, you will see that the inclusion of PM did not affect the gaseous effect size estimates either.
10. p. 8-82, lines 11-20 – It would be appropriate to add an abridged caveat discussed in my comment 6 here.
11. p. 8-84, lines 2-3 – This conclusion is out of place before the VA and AHSMOG are even discussed.
12. p. 8-88, line 29, p. 8-99, lines 27-28, and p. 8-100, line 7 – These are misleading understatement that obscure the fact that those with a high school education or more showed no statistically significant response.
13. p. 8-101 to p. 8-106 – The discussion of the AHSMOG study is not very balanced. The bottom line of this study is that it shows very little indication of a PM/mortality relationship. However, the Agency focuses on the few subsets of analyses that show a positive relationship and tries to rationalize why the rest of the analyses fail to show a positive response.
14. p. 8-111, line 29 – How does subject size account for different results?
15. p. 8-113, lines 13-16 – For these same reasons, this make the VA cohort a susceptible population which should give special insights into cardiac responses.
16. p. 8-114, lines 22-23 - Why would cohort depletion be an issue only in the VA study?
17. p. 8-116, lines 1-12 – This clearly comes off as blatant case of cherry-picking the results that support the Agency’s position.
18. p. 8-118, lines 14-17 – The reasons for not including the VA results in Tables 8-15 and 8-16 defy logic. This is another example of selective use (or in this case omission) of the data to support the Agency’s position.
19. p. 8-121, lines 1-4 – This is only true if the VA and AHSMOG are excluded.
20. p. 8-124, line 20 to p. 8-125, line 24 – There are so many flaws in the Hoek et al study that it should not be used to support any arguments. First of all, NO₂ cannot be used as a tracer of fresh vehicle exhaust since it is a secondary product. As a result, its concentrations tend to be more homogeneous than a primary emission. NO or CO would have been a much more reliable tracer. Second, and more importantly, Hoek et al manufactured the concentration fields for BS and NO₂ by using unvalidated statistical

methods and data from two short sampling studies in 1995. They then extrapolated 1987-1990 monitoring data to represent the ambient air quality during his 1986-1994 health study. This is so far removed from actual exposure data, that the study should just be ignored.

21. p. 8-130, line 25 – I think a few more words on the education effect are in order explaining that the only significant effect is seen with the 20% of the cohort who did not finish high school.
22. p. 8-130, line 7 to p. 8-133, line 9 – It needs to be mentioned that most of the AHSMOG results disagree with the other two studies. In addition, the VA's no effects results need to be included.
23. p. 8-227, line 1 to p. 8-229, line 6 – This section does a good job summarizing the HEI Commentary. However, it leaves the reader hanging. The last bullet on page 8-229 is powerful and has potentially wide-ranging implications concerning the validity of time-series studies results. This bullet plus the results presented in the Koop and Tole paper cited above must be addressed because they potentially undermine the validity of the time-series results.
24. p. 8-237, lines 17-25 and Figure 8-16 – Again, I refer the authors to figures 12 and 14-16 in the revised NMMAPS report. These figures show that there is one lag for each of the gases that show a significant correlation and an effect equal to or greater than PM. As co-pollutants are added, the effect size estimates change little. Consequently, using figures 8-16 to 8-19 to make decisions on confounders, is not valid unless the co-pollutants are treated in the same way.
25. p. 8-245, section 8.4.3.4 – I am happy to see this section added, but it leaves me hanging. Should we be concerned about bioaerosol confounding or not?
26. p. 8-246, section 8.4.3.5 – I am ecstatic to see this discussion of meteorological variables and time trend model specifications. However, after reading it, I felt I was left hanging again. What are the implications?
27. p. 8-256, line 6 – Do the Smoyer et al papers employ GAM?
28. p. 294, lines 24-28 – Again for the reasons stated above, this sounds like a recipe for cherry picking.
29. p. 8-295, section 8.4.6.3 – My above comment 6 applies to this section as well.
30. p. 8-310, line 28 – The heterogeneity shows itself in these studies by the fact that the specifications of the models for each city are very different. This should be pointed out.
31. p. 8-311, lines 7-16 – It should be pointed out that the results of most of these studies are unreliable because of the GAM issue.

32. p. 8-311, lines 19-20 – Again, “newly apparent heterogeneity” is a misnomer because the older studies displayed model specification heterogeneity.
33. p. 8-312, lines 7-27 – This explanation of heterogeneity needs some graphs to back it up.
34. p. 8-323, line 11 – Given the model specificity issue, how can one claim that the reported multi-city estimates are more precise?
35. p. 8-332, lines 19-29 – It should be pointed out that these are the Agencies conclusions because they ignore 2 of the long-term studies.

Chapter 9

1. p. 9-20, lines 29-31 – By using only single pollutant studies, some of the heterogeneity of results is masked.
2. figures 9-5 and 9-6 – The figure caption needs to explain what the lengths of the vertical lines mean.
3. p. 9-26, lines 1-15 - Somewhere in this section, it should be pointed out that Pb was used as a tracer for vehicle exhaust in these studies that utilized relatively old air quality data. Presently, and for the last 10 years or so, we can no longer use lead as a tracer of vehicles, because highway vehicles no longer burn leaded gasoline. In those intervening years, vehicle PM emissions have declined significantly as the composition has changed as well. Consequently any inferences drawn for these studies, may have no applicability to situation today.
4. p 9-28, lines 1 and 2 – The VA results were consistently non-significant.
5. p. 9-28, lines 6-6 – If you are going to ignore the VA and AHSMOG studies, they at least deserve a short summary of their results.
6. p. 9-29, line 9 to p. 9-30, line 8 – This section is very inadequate. It fails to convey the importance of the model specificity issue and the concerns raised by the HEI Special committee. It needs to be expanded to convey these concerns.
7. p. 9-31, lines 8-11 - I refer the authors to figures 12 and 14-16 in the revised NMMAPS report. These figures show that there is one lag for each of the gases that show a significant correlation and an effect equal to or greater than PM. As co-pollutants are added, the effect size estimates change little. Consequently, the argument made by the Agency here is not valid unless the gases are examined in the same way as PM.
8. p. 9-32, lines 25-29 – If the $PM_{2.5}$ is dominated by NO_3 , the infiltration factor would be low.

9. p. 9-33, lines 14-15 and lines 30-31 – This statement cannot be made without the appropriate caveat. The test that was used had low statistical power so it was not conclusive.
10. p. 9-58, line 14- Is this referring to the Hoek et al study? If so, see my comment 20 on Chapter 8.
11. p. 9-62, lines 23-24 – What was the concentration of the sulfate-coated carbon black?
12. p. 9-65, line 5 – Metals do not make up a substantial part of the mass.
13. p. 9-81, line 24 to p. 9-82, line 3 – On Figures 8-24 to 8-28, I do not understand where the Dominici (2003) estimates came from. Shouldn't they be the same as the ones shown in Figure 8-1?
14. p. 9-85, line 4 to 9-86, line 4 – This section is not very convincing.
15. p. 9-93, lines 22-23 – The Gwynn and Thurston reference should not be used because it is based on the flawed GAM analysis.
16. p. 9-94, lines 25-27 – This is pure speculation.
17. p. 9-94, line 28 to p. 9-95, line 2 – As I said before, the Hoek et al study is so poorly done, it should not be relied on. See my comment 20 on chapter 8.
18. p. 9-95, lines 5-14 – This summary and conclusions section is very weak as evidenced by the number of qualifiers used. It is not at all convincing.
19. p. 9-100, lines 22-25 – How can this be said in light of the previous sentence? How can this be said in light of the model specificity issues?
20. p. 9-100, lines 25-27 – How can this be said with such certainty when two of the prospective cohort studies were ignored?
21. p. 9-116, line 30 – Delete the rest of the sentence after the word “gases.” The rest is speculation and this document does not need to go there.

Additional Comments on Chapter 9 of the June 2004 Criteria Document for Particulate Matter

George T. Wolff
(7/27/04)

Based on the discussions at the July 20-21 CASAC meeting and the written comments of other panelists, I would like to add a few other points.

Section 9.2.2

Although I disagree with the Panel's decision not to include the Koop and Tole (2004) paper in the CD, the issue of model uncertainty/model selection should still be rigorously discussed in both chapter 8 and chapter 9. The idea that the results of a single model based on sequential hypothesis testing will under-represent the overall uncertainty is not new to the Koop and Tole paper. Similarly, if important explanatory variables are omitted either because of model selection decisions based on imperfect knowledge or a lack of appropriate measurements, the results of the reported model will under-represent the overall uncertainty.

As Jon Samet indicated, there is not any one "true" model. The discussion of the decision to emphasize the results of selected single-pollutant models needs to acknowledge the potential bias and uncertainty as a result of that decision.

The presentation of results in this section in the text and in figures 9.5 and 9.6 hinges on how one considers the multi-city studies together with the individual city studies. For example, if the NMMAPS mortality results are viewed as 88 or 90 point estimates of which only a couple are statistically significant, one gets one impression of the strength and consistency of the data. If one focuses on the pooled estimate, one gets a different impression. I would argue that both views are important and should be presented. One way to do this is to include the range of individual point estimates whenever a pooled multi-city result is given.

Section 9.2.3

The idea of adding a table or tables to summarize the toxicological results by endpoint has merit. However, as Fred Miller indicated, the tables need to provide a perspective on the doses used in the relevant tox studies as compared to ambient doses. The method of exposure also matters so whether the evidence is from inhalation, instillation or in vitro studies needs to be listed too.

The material in Appendix 7A responds to repeated requests by the Panel on this subject. However, it would be particularly helpful if additional findings from the calculations can be brought out in the Appendix and then brought into the discussion in Chapter 9. For example, representative doses for comparison with the acute and chronic studies can be derived from the material. For comparison with acute epi studies, we are interested in the deposited and retained doses in humans in one day or up to several days for total fine PM and PM components. The amounts per lung surface area and per kg body weight should be reported. The caveat that

localized doses may exceed the average should also be included. For comparison with chronic epi results, typical deposited and retained doses will be much greater. (see Figures 7A-8 and 7A-10, for example.)

In both cases, the dose from ambient PM is added to the dose already in the lung from earlier exposures. For acute exposures, since the chapter argues that exposures to ambient PM are generally independent of exposures to indoor-source PM, the small increment from ambient PM is the relevant potential cause of the health outcomes implicated by the epi studies. However, for chronic studies, the total dose of particles from outdoor, indoor, active smoking, passive smoking, occupational sources, and the personal cloud all contribute to the chronic burden. As Dr. Vedal pointed out, the use of central monitor measurements to characterize chronic exposures is a significant issue. Whether we can assume that the chronic burden from all non-ambient sources is the same from city to city is an important research question. Perhaps differences in the overall chronic burden within the cohorts can explain some of the differences among the chronic studies.

To put the in vitro results in perspective, some comparisons in terms of mass or number of particles per cell should be added to give the reader information on the general order of magnitude difference in doses between the in vitro literature and typical acute human exposures.

The point made on page 9-60 that, based on tox studies, some types of particles are more toxic than others, needs elaboration. It fits in with statements in chapter 8 that some components may be benign at current ambient concentrations. The discussion last week by various panelists that we should be thinking about or moving toward regional standards or standards for specific components as indicators of different sources, all fits in with the general understanding that all particles are not alike in terms of their toxicity and effects. It is also relevant to general point 5 raised in Roger McClellan's written comments. This is an important finding from the science that needs to be clearly stated in the CD.

It is also a major factor behind the reluctance of some panelists to push for stringent coarse standards. Crustal components and bioaerosols are two major categories of coarse particles but the evidence for direct crustal effects is limited and bioaerosols, even though they may vary substantially in toxicity, are generally thought to be not conducive or subject to control.

Section on coherence on pages 9-81 to 9-85

This is an important section that needs to pull together and compare the results from epi, tox, and dosimetry studies. The dosimetry examples can be particularly useful in this context. The discussion of the Utah Valley results as compelling needs to be re-considered in terms of the new dosimetric comparisons in 7A that show how large the instilled doses are compare to daily or even weekly inhalation doses. Dr. Oberdorster's comment on the particularly high dose rate for the instillation compared to Utah Valley ambient PM levels during the period should also be included.

There is only one paragraph on page 9-84 discussing coherence in relation to chronic effects. Although the ACS and Six-City Studies reported associations with cardiopulmonary mortality,

the HEI re-analysis pointed out that the association was with cardiovascular and not respiratory mortality. This distinction is important. The text argues that there have not been tox studies of chronic PM exposure or epi studies investigating chronic cardiovascular disease. However, there is a substantial body of occupational PM information and what it says or does not say about chronic cardiovascular health outcomes would be enlightening. This section should also discuss the variation in the chronic mortality studies in relation to the dosimetric considerations noted above. The gender difference in the AHSMOG cohort (with a tendency for positive results in males and negative or protective effects in females) is too large to be accounted for by a small difference in time spent outdoors between the genders. The VA cohort is a susceptible sub-population so its negative association with PM is puzzling if the ACS result is due to ambient PM differences. While, the text acknowledges that that evidence of coherence in the chronic studies is “somewhat limited,” consideration of the factors I have noted renders the evidence as extremely limited.

For the acute studies, the text should include and discuss the dosimetric comparisons noted above.

Finally, the question of consistency of results needs to be addressed. For example, the mixed, inconsistent, and sometimes conflicting results in cardiovascular studies needs to be acknowledged and discussed in chapter 9 both earlier in Section 9.2.3 and in the coherence discussion.

Also, the EMA comments prepared by Dr. Vendetti should be accommodated.

A final thought on biological plausibility

As the Agency goes through the various CD's for different pollutants, the question of what to do with a growing number of pollutant/mortality and morbidity associations for each of the criteria pollutants will come to center stage. While it is critical that EPA and the scientific community rigorously evaluate biological plausibility in terms of concentrations present and nature of effects for PM, perhaps such an effort should be extended to include all the criteria pollutants. I do not know what form this might take or what forum might be used to carry it out, but leaving the issue to consideration in separate CDs leaves too many degrees of freedom, from missing effects because they are blamed on another possible causal pollutant to double or triple counting of mortality from air pollution and blaming it on each pollutant separately.

NOTICE

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