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REVIEW OF EPA's HEALTH ASSESSMENT DOCUMENT FOR DIESEL EXHAUST (EPA 600/8-90/057E)

REVIEW BY THE CLEAN AIR SCIENTIFIC ADVISORY COMMITTEE (CASAC)

December 19, 2000

EPA-SAB-CASAC-01-003

Honorable Carol M. Browner
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Subject: Clean Air Scientific Advisory Committee (CASAC) Review of EPA's Health Assessment Document for Diesel Exhaust (EPA 600/8-90/057E)

Dear Ms. Browner:

The Clean Air Scientific Advisory Committee (CASAC, also referred to as the Committee) of the EPA Science Advisory Board, supplemented by expert consultants (together referred to as the Panel), met on October 12-13, 2000 to review the July 2000 draft document, *Health Assessment Document for Diesel Exhaust* (EPA 600/8-90/057E), in a public meeting in Alexandria VA. This draft document was prepared by EPA's National Center for Environmental Assessment (NCEA), Washington, DC

An SAB Subcommittee conducted an initial review of the diesel topic in 1990. Subsequently, CASAC reviewed drafts of the diesel health assessment document in 1995 and 1998, finding in both cases that the document was not yet scientifically adequate for making regulatory decisions. A consultation between the Panel and NCEA Staff (hereafter referred to as Staff) was held on June 10, 1999 regarding the development of the next draft. On December 1, 1999, CASAC reviewed the draft document and found it improved, but not sufficient to warrant closure.

During the October 2000 meeting, numerous suggestions were offered for additional revisions to improve the document's accurate and complete portrayal of current knowledge. Several key issues were discussed, and agreement between the Committee and Staff was reached on approaches to be taken to making changes addressing all key issues. Two issues engendered extended discussion.

It was agreed that two approaches would be taken to characterizing the level of long-term environmental exposure considered acceptably free from significant non-cancer health risk. A reference concentration (RfC) would be derived as before, but would include an interspecies uncertainty factor resulting in a value of approximately 5 $\mu g/m^3$. It was agreed that linkages between risks from diesel particulate matter (DPM) and ambient particulate matter (PM) would also be

discussed, concluding that an annual national ambient air quality standard (NAAQS) for $PM_{2.5}$ would be considered adequately protective for long-term exposures to ambient DPM.

The inclusion of a range of cancer risk values provides a perspective on the possible range of lung cancer risk from environmental exposures was strongly debated. There were concerns for the conflict between inclusion of a range and the decision not to adopt a unit risk value for cancer, and for the likely misuse of the values despite Agency disclaimers. It was agreed that the range would be included, but accompanied by clear caveats and disclaimers concerning the uncertainty of the risk values, the use of the values, and the fact that the possible lower end of the risk range includes zero.

With mixed recommendations from its consultants, the Committee reached unanimous closure on the document on October 13th, based on assurances by Agency staff that key revisions would be made as agreed and attention would also be given to the numerous more minor issues raised by the Panel.

CASAC compliments EPA Staff for their strong effort to respond to the Panel's recommendations in developing the revised draft. With further, final revisions, the document will constitute an acceptably accurate and complete summary of current knowledge concerning the health effects of diesel emissions.

We look forward to your response to the advice we have given in this report and seeing the final version of the Diesel Health Assessment so that it can provide scientific input to the future decisions of the Agency.

Sincerely,

/s/

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

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U.S. Environmental Protection Agency
Science Advisory Board
Clean Air Scientific Advisory Committee (CASAC)
Diesel Review Panel

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[1] Appointment as Chair of CASAC ended on October 30, 2000. Appointed *ex officio* Past Chair until September 30, 2001.

[2] CASAC Members are experts appointed by the Administrator to two-year terms to serve on the Clean Air Scientific Advisory Committee.

[3] Appointed as Chair of CASAC on October 30, 2000.

[4] Resigned from CASAC on September 28, 2000.

[5] Appointment as Member of CASAC ended on October 30, 2000.

[6] CASAC Consultants are experts appointed by the Science Advisory Board Staff Director to a one-year term to serve on *ad hoc* Panels formed to address a particular issue; in this case, the CASAC Review of EPA's Health Assessment Document for Diesel Exhaust.

[7] Federal Expert.

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1. EXECUTIVE SUMMARY

The Clean Air Scientific Advisory Committee (CASAC), of the EPA Science Advisory Board, supplemented by expert consultants met on October 12-13, 2000 to review the July 2000 draft document, *Health Assessment Document for Diesel Exhaust* (EPA 600/8-90/057E), in a pubic meeting in Alexandria, VA. This review followed reviews of previous drafts in 1995, 1998, and 1999. The Committee found the July 2000 draft, pending key revisions agreed upon at the meeting (summarized below) and numerous minor editorial changes, to be an adequate summary of current knowledge concerning the health effects of diesel engine emissions.

The draft was improved over the last draft, and the Committee complimented Staff for its strong effort to take the Panel's previous comments and recommendations into consideration. The Panel approved of the general framework of the document. Two of the key issues raised at the last review were satisfactorily addressed in accordance with the Committee's guidance. First, the revision eliminated the use of a different health effect, immunological responses, as a basis for adjusting the reference concentration (RfC) for non-cancer effects based on lung pathology. Second, the revision changed the descriptive characterization of cancer hazard from long term environmental exposures from "highly likely" to "likely".

Numerous suggestions were offered for additional revisions throughout the document to improve its accurate and complete portrayal of current knowledge. Agreement between the Committee and Staff was reached on approaches to making changes addressing all key issues.

It was agreed that two approaches would be taken to characterizing the level of long-term environmental exposure considered acceptably free from significant non-cancer health risk. An RfC would be derived as before, but including a factor for uncertainty in interspecies extrapolation and resulting in a value of approximately 5 $\mu g/m^3$. It was agreed that linkages between risks from diesel particulate matter (DPM) and ambient PM would also be discussed, concluding that an annual NAAQS for $PM_{2.5}$ would be considered adequately protective for ambient DPM.

The inclusion of a range of cancer risk values to provide a perspective on the possible range of lung cancer risk from environmental exposures was debated. There were concerns that inclusion of the range could be perceived as inconsistent with the decision not to adopt a unit risk value for cancer, and for the likely misuse of the values despite Agency disclaimers. It was agreed that the range would be included, but accompanied by clear caveats and disclaimers concerning the uncertainty of risk, the use of the risk perspective values, and the fact that the possible lower end of the risk range includes zero.

With mixed recommendations from its consultants[1], the Committee reached unanimous closure on the document, pending assurances that the above key revisions would be made and attention would be given to incorporating numerous more minor changes suggested in the individual Panelist's comments.

[1] The closure options presented to the Panel by the Panel Chair were to: a) close on the draft document without needing to see it again; or b) not close on the draft document if they desired to review additional rewrites (this latter option would require an additional meeting). Three of the six consultants indicated that they wished to see how EPA characterized the results of the Panel discussions in certain sections of the draft document, as a result, these three consultants were not able to fully close on the draft document. All six of the CASAC Members present (the seventh Member had resigned prior to the review) choose to close on the draft document without formally seeing it again, assuming that EPA would make a good faith effort to incorporate appropriate updates as discussed during the meeting on October 12-13, 2000.

2. INTRODUCTION

2.1 Introduction

The Clean Air Scientific Advisory Committee (CASAC) Diesel Review Panel (Members plus expert Consultants) reviewed the Agency's revised draft Health Assessment Document for Diesel Engine Exhaust (EPA, 2000) on October 12-13, 2000 in Alexandria, VA. The draft review document was prepared by the Agency's National Center for Environmental Assessment (NCEA) - Washington, DC Office.

The diesel topic was first reviewed by a Subcommittee of the Science Advisory Board in 1990. This initial effort was followed in 1995 when the first CASAC Diesel Review Panel (Members plus expert Consultants) conducted a peer review of the December 1994 version of the draft diesel assessment. As a result of that review, the CASAC recommendations focused on: a) the use of specific uncertainty factors in deriving the RfC (reference concentration) value for protecting from adverse noncancer respiratory effects; b) the minimal scientific support for using rat bioassay data for estimating human cancer risks; and c) the outdated nature of information in several chapters. The Committee also made numerous suggestions and recommendations for improving the draft document, asking to review the revised document when it was ready. These recommendations are covered in detail in the CASAC report of that review (CASAC, 1995).

The resultant revised draft diesel assessment was then reviewed by a new CASAC Diesel Review Panel at a meeting on May 5-6, 1998. At that meeting, NCEA provided CASAC with a listing that identified the disposition of the significant recommendations that had been made by CASAC in 1995 (CASAC, 1995). The CASAC Diesel Review Panel that was created for this 1998 review included a number of Members and Consultants who served on the 1995 Panel as well as new panelists to ensure that the composition of the review panel would be fresh and objective. This is the standard practice of the SAB and is consistent with the provisions of the Agency's 1994 Peer Review Policy and the 1998 Peer Review Handbook (EPA, 1998). Panelists were asked to provided written comments on the questions in the charge as well as specific chapters that they had been assigned for review. These recommendations are covered in detail in the CASAC report of that review (CASAC, 1998). The Committee could not close on the draft and asked that the Agency make the requested revisions and schedule another peer review meeting.

On June 10, 1999, the Committee held a Consultation with NCEA Staff regarding the development of the next revision of the draft diesel document (CASAC, 1999a). This was done as a precursor to the next full peer review planned for later that year. On December 1, 1999, CASAC Diesel Review Panel met in Research Triangle Park, NC to conduct a peer review of the Agency's revised draft Health Assessment Document for Diesel Engine Emissions (EPA, 1999). As a result of that review, it was clearly apparent that Staff had made a strong effort to respond to the Panel's earlier

recommendations in developing the revised draft. However, the number of major and minor remaining criticisms and recommendations raised by the Panel once again precluded closure on the draft document. In particular, there was substantial concern for the approach taken to deriving the uncertainty factors used in calculating the reference concentration value (RfC) for noncancer health effects. Secondly, the majority of the Panel disagreed with the Agency's use of the description "highly likely" to portray cancer hazard from long-term environmental exposures. These recommendations, and others, are covered in detail in the CASAC report of that review (CASAC, 1999b). The CASAC asked to see a further revision of the draft document, which is the subject of this current CASAC report.

2.2 Charge

The chief purpose of this review was to determine whether or not changes made in response to previous CASAC guidance resulted in a revised document satisfactory for closure. No other specific charge questions or issues were raised by Staff.

3. COMMENTS BY CASAC ON EACH CHAPTER

In developing the final version of the document, we advise the Agency to consider the full range of suggestions contained in the detailed written comments of the individual Panel members (see Appendix A), the summary minutes of the meeting, and comments made during the meeting. Because a full transcript of the meeting was not created, Staff are encouraged to interact with the Committee Chair as may be necessary to ensure that key revisions are consistent with the intent of the agreements reached at the meeting. Only summary comments concerning key issues are contained in this report.

3.1 Chapter 1: Executive Summary

This chapter will need to be examined carefully and revised as necessary to ensure that it reflects changes made in subsequent chapters.

It would be useful to include a statement on the motivation for developing this Hazard Assessment Document and its relationship to regulatory decision-making.

It would be useful to briefly summarize emissions trends and the contribution of diesel emissions to the nation's emissions inventories and pollutant burden.

3.2 Chapter 2: Diesel Emissions, Characterization, Atmospheric Transformation, and Exposures

This chapter is much improved. The Panel offered several additional references for inclusion in the final version.

Tables summarizing emissions trends and the contribution of diesel particulate matter (DPM) and nitrogen oxides to the total emissions inventory should be added to the chapter, in order to better place the contribution of diesels into context.

The chapter should make clearer that DPM is a subset of ambient PM, rather than something separate from ambient PM, as the present wording appears to suggest in several places. It can be clearly stated that although the composition and potential toxicity of DPM may differ from those of the composite ambient PM, DPM is a ubiquitous component of ambient PM.

Different techniques have been used for measuring elemental carbon and organic carbon, and they yield significantly different results. Without specification of the measurement method, results from different reports may not be directly comparable. Indications of the measurement method should be added to citations of results from different studies and comparisons among them.

The chapter appropriately mentions differences in fuels used in on-road, off-road, and railroad diesel engines. However this and subsequent chapters fail to tie these differences to their potential

implications for health hazards. For example, would differences between on-road and railroad diesel fuels have any implications for the possible interpretation or comparisons of epidemiological results from truck drivers and railroad workers? Stationary sources should also be discussed. It also does not indicate that the changes made in on-road diesels to reduce their emissions may have also changed the toxicological characteristics of those emissions (for example, reduced amounts of organic carbon associated with the particles).

3.3 Chapter 3: Dosimetry of Diesel Exhaust Particles in the Respiratory Tract

The fact that DPM exhibit little hygroscopic growth has bearing on the estimation of deposition in the respiratory tract, and should be mentioned.

The portrayal of deposition should be expanded by considering the entire respiratory tract, rather than just focusing on deposition in the lung. Substantial deposition also occurs elsewhere, and this knowledge is important to placing non-lung health effects into context (e.g., nasal deposition and nasal immunological responses). Figures illustrating the relationship between regional deposition fraction and particle size are readily available, and an example should be included.

The discussion of different deposition models should be accompanied by a comparative presentation of example results using the different models. For example, it would help to place the deposition assumptions and results of the model used to derive the RfC into context regarding other broadly-accepted models like those of the NCRP or ICRP.

The discussion of interspecies differences in the interstitialization of particles should note that, although differences between the proportion of particles in the interstitium of rats and non-human primates have been observed, the observations have been at single times after chronic exposure, and it is possible that comparable amounts of material enter the interstitium of rats, but move more rapidly to lymph nodes and other locations than in primates. It should also be stated that the information cited in regard to interstitialization is derived from high-dose exposures, and that no such information exists for exposures at environmental levels. Points were raised in individual comments that would enhance the discussion of how interstitialization is treated in the Yu model.

This chapter still does not adequately portray the plausible doses of organic compounds to airway or pulmonary cells that might result from either environmental or occupational exposures. Some straightforward "order of magnitude" calculations could be added, and would help place the subsequent information on high-dose *in vitro* mutagenicity test results into a more useful perspective. This issue was raised repeatedly in reviews of previous drafts, and has still not been adequately addressed.

3.4 Chapter 4: Mutagenicity of Diesel Exhaust

It would be useful to bring the discussion of our understanding of the linkages between mutagenicity and carcinogenicity up to the front of the chapter. This should be followed by the information briefly describing the history of diesel-related mutagenicity research, which could be usefully, but still succinctly, expanded as suggested by individual reviewer comments.

As noted above, the issue of the relationship between doses used in mutagenicity assays and plausible doses received from environmental exposures should be discussed. The chapter does a disservice by not placing dose into better perspective.

3.5 Chapter 5: Noncancer Health Effects of Diesel Exhaust

This chapter fails to mention the exposure or dose used in many of the studies cited. Without some indication of dose, information on health responses has little value. The relationship of experimental doses to those from resulting from plausible human exposures is key to understanding whether responses are likely to be of public health concern.

The chapter contains a good breadth of information on non-cancer health issues; however, there is insufficient depth of interpretation of much of the information. The superficial treatment of the information leads to both under- and over-interpretations. A few examples follow. Many of the cellular and chemical changes listed are biological markers that are consistent with asthma, but the studies do not demonstrate that asthma was produced. Many of the differences between results of animal studies are more likely due to differences in study design, rather than to true interspecies differences, as presently implied. The chapter appears ignorant of the implications of the important differences between studies. The discussion of the increase in immune responses caused by pyrene implies that pyrene is a concern. The discussion does not clarify that pyrene was used as a single model compound and was not compared to other compounds. It is not mentioned that other results indicate that adjuvant activity is characteristic of multiple organic species, and among multiple combustion emissions.

The chapter states wrongly that there have been no well-controlled chamber studies. Studies are cited in the Panelists comments.

The treatment of roadside asthma studies is too superficial. Present information should be described more thoroughly, including a better distinction between asthma prevalence and exacerbation of asthmatic responses.

A number of key references to be considered for inclusion in the final document are offered in individual Panelist's comments (see Appendix A).

3.6 Chapter 6: Quantitative Approaches to Estimating Human Noncancer Health Risks of Diesel Exhaust

The presentation of information linking effects of DPM to those of ambient PM is improved, but the comparison remains difficult. The contribution to the difficulty in making the linkage of the different types of experimental approaches taken to DPM and ambient PM should be explained. The suggestions in individual Panelist's comments for additional citations for this material, and for discussing their implications, should be incorporated.

The information contained in the appendix on benchmark concentration analysis should be discussed in a paragraph, rather than the present single sentence.

The description of the derivation of the human equivalent concentration (HEC) needs further clarification. First, as agreed at the meeting, the section can be enhanced substantially by the addition of a table listing the key input parameters and values used for rats and humans in the Yu model. Second, one can determine from the appendix that the different patterns of rat exposures were normalized to continuous exposures to derive the HEC, but this fact and the uncertainties thus introduced into the extrapolation need to be stated clearly in the text. The statement that time averaging was not part of the assessment appears in conflict with the use of time averaging in deriving the HEC. Third, it should also be explained in the text why the relationship between rat exposure concentration and HEC are not proportional over the concentration range listed in Table 6-2.

The approach to be taken to characterizing a safe level for noncancer effects of long-term exposure was discussed at length. Staff had responded to the previous criticism of using an uncertainty factor based on immunological responses to modify the no-effects HEC based on rat lung pathology by removing the factor; thus increasing the reference concentration (RfC) from 5 to 14 $\mu g/m^3$. There was general agreement that immunological effects may possibly supersede lung pathology as the critical health concern, but that: 1) immunological responses were more likely a concern for acute, rather than chronic, exposures; and 2) present knowledge was insufficient for deriving a reference concentration (RfC) for DPM based on immunological responses. There was also general agreement that it was reasonable to retain some form of uncertainty factor for interspecies extrapolation.

Staff had also responded to the request to expand on the linkage between the safe level of DPM and the proposed annual NAAQS for $PM_{2.5}$. It was generally agreed that some form of such a comparison should be retained, but that current knowledge was insufficient to describe the relative potencies of DPM and other components of $PM_{2.5}$ with confidence.

After discussing several options, agreement was reached between the Committee and Staff to deal with these issues by presenting two perspectives, along with caveats regarding the uncertainties involved.

RfC for DPM: An RfC derived in the same manner as that in the draft and based on rat lung pathology will be included. An uncertainty factor of 3 for interspecies extrapolation will be

used, together with a factor of 10 for differences in individual sensitivity, resulting in an RfC of 5 $\mu g/m^3$.

DPM vs. $PM_{2.5}$: A discussion will be included which draws the general conclusion that, as long as DPM continues to constitute it's approximate present proportion of $PM_{2.5}$, an annual $PM_{2.5}$ standard would be considered adequately protective for DPM.

3.7 Chapter 7: Carcinogenicity of Diesel Exhaust

The value of the Hill criteria for supporting the Agency's case for cancer causation was questioned, especially considering their reliance on the Rothman interpretation of the criteria for explaining why individual criteria did not have to be met. Perhaps only the consistency and biological plausibility criteria have been clearly met; there was general agreement that the dose-response criterion has not been clearly met.

Latency of effect remains a key issue in interpreting the present database to indicate that diesel emissions are carcinogenic in an exposure-related manner. Latency should be discussed more explicitly in regard to the studies cited, indicating which studies provide useful information on latency , what range of latency is present in each, and which studies provide no information on latency. This information might best be provided in a table.

The brief discussion of the California EPA and Crump analyses of the epidemiological data should be expanded to describe the differences, and the more recent analysis organized by the Health Effects Institute should also be included and described.

There continued to be concern for the use of the rat inhalation studies as part of the weight of evidence argument, as had been expressed during previous reviews. It was agreed that other laboratory results provided sufficient biological plausibility for a cancer hazard. Staff agreed to exclude the rat inhalation results as part of the weight of evidence for carcinogenicity, although the summary characterization of the evidence would not be changed as a result.

The conclusion in the weight of evidence section that diesel exhaust is likely to be carcinogenic to humans is consistent with the Committee's previous guidance. There remained, however, mixed views concerning: 1) the use of the term exhaust instead of citing a component, or components, of exhaust; and 2) the further characterization, at any exposure condition. The former could be misinterpreted to suggest that no clean-up strategy could reduce concern as long as something was emitted, even if only water and carbon dioxide. The latter implies a clearer understanding of the exposure-response relationship than presently exists, and should be clarified as a default assumption in the absence of complete information.

3.8 Chapter 8: Dose-Response Assessment: Carcinogenic Effects

The appendix on epidemiological studies warrants a summary paragraph, rather than the present single sentence.

There should be a clearer, more methodical, more explicit summary of the uncertainties in interpreting the epidemiological database with respect to dose-response. This summary will enhance the reader's understanding of the caveats given later regarding the range of risk values.

The Committee continued to agree with Staff's decision not to adopt a unit risk value. It was agreed that no single existing data set, or combination of existing data sets, allows for the calculation of an estimate of unit cancer risk with acceptable confidence. It was felt unlikely that continued evaluation of data sets from past epidemiological studies will resolve the uncertainties to a satisfactory degree, due primarily to the lack of exposure information. There were mixed views regarding the likelihood that future studies will provide an acceptable unit risk value applicable to environmental exposures.

The inclusion of a range of cancer risk values to provide a perspective of the possible range of lung cancer risk from environmental exposures to DE was a major topic of discussion and a pivotal issue in the Committee's decision to close on the document. The range first appeared in Chapter 8, and appeared again in Chapter 9. Staff made clear its intent that its listing of the values was not to be interpreted as the Agency's endorsement of their use as unit risk values. There were mixed views among both the Committee and the Consultants regarding the appropriateness of including the range; however, there was general agreement that, despite Agency disclaimers, the publication of the range would likely be cited as endorsement of the values as unit risks for estimating cancer deaths. Consensus was already established that no unit risk value could be calculated with sufficient confidence to be presented in the document as an Agency position. The difficult issue, therefore, was the conflict between the use of the values to portray a possible range of risk and the agreement that no satisfactory unit risk value could be selected.

Staff emphasized that the range should be included in order to illustrate that the most likely magnitude of risk is sufficient to be of public health concern; i.e., that the risk is not negligible and warrants continued action to control exposures to diesel emissions. Staff did not find acceptable the recommendations offered by some Panelists for relying solely on a text characterization of likely risk.

The Panel generally, but not unanimously agreed that the inclusion of the range of values would not prevent a recommendation for closure on the document, pending the accompanying inclusion of satisfactory caveats and disclaimers. The nature of the caveats was discussed and specific language was offered by some Panelists. Although agreement was not reached on specific language, it was agreed that the disclaimers would include clear statements that: 1) that the values were attended by considerable unresolved uncertainty; 2) that their inclusion in the document did not constitute Agency endorsement of their validity as unit risk values; 3) that the values are not proposed as useful for estimating numbers of cancer deaths; and 4) that the range of potential risk from environmental exposures was very broad and included at its lower bound the possibility of zero risk.

3.9 Chapter 9: Characterization of Potential Human Health Effects of Diesel Exhaust: Hazard and Dose-Response Assessments

This chapter largely recaps the preceding material. Several comments and recommendations are contained in the individual comments of the Panelists, and should be considered in developing the final document. Most of these comments repeat and reinforce issues raised in other chapters.

The basis for the statement that carcinogenicity is related to particle size is unclear. The meaning of the statement, which only occurs in this chapter, is not explained and no data are given to support the claim. The statement should be removed.

4. CONCLUSIONS

The consultants offered mixed recommendations regarding closure on the document, with some recommending re-review of some or all of the changes made in response to this review.

The Committee was unanimous in recommending closure pending Staff's careful attention to all comments offered at the meeting and in writing, and pending the revisions to which the Committee and Staff agreed at the meeting. It was the Committee's view that, despite the considerable remaining uncertainties regarding the health impacts of diesel emissions, the document as appropriately revised will constitute a reasonable portrayal of current knowledge in the field.

REFERENCES CITED

CASAC. 1995. *Review of the Diesel Health Assessment*, EPA-SAB-CASAC-LTR-95-003, Clean Air Scientific Advisory Committee, US EPA Science Advisory Board, Washington, DC.

CASAC. 1998. *CASAC Review of the Draft Diesel Health Assessment*, EPA-SAB-CASAC-99-001. Clean Air Scientific Advisory Committee, US EPA Science Advisory Board, Washington, DC, October 7, 1998.

CASAC. 1999a. *Notification of a Consultation on the Diesel Health Assessment*, EPA-SAB-CASAC-CON-99-005, Clean Air Scientific Advisory Committee, US EPA Science Advisory Board, Washington, DC, July 9, 1999.

CASAC. 1999b. *CASAC Review of the Draft Diesel Health Assessment Document*, EPA-SAB-CASAC-00-004. Clean Air Scientific Advisory Committee, US EPA Science Advisory Board, Washington, DC, February 4, 2000.

EPA. 1998. *Peer Review Handbook*. EPA 100-B-98-001, Science Policy Council, Office of Research and Development, US Environmental Protection Agency, Washington, DC, January 1998.

EPA. 1999. *Health Assessment Document for Diesel Emissions* (EPA 600/8-90/057D), US EPA, Office of Research and Development, Washington, DC, November 1999.

EPA. 2000. *Health Assessment Document for Diesel Exhaust* (EPA 600/8-90/057E), US EPA, Office of Research and Development, Washington, DC, July 2000.

Please note: The above referenced CASAC reports are available on the SAB website at www.epa.gov.sab under the REPORTS heading. The EPA reports are available from the Office of Research and Development (ORD) under www.epa.gov/ncea or www.epa.gov/ORD/spc/2polprog.htm.

APPENDIX A - INDIVIDUAL PANELIST WRITTEN COMMENTS

Note: These are the final written comments provided by individual Panelists following the October 12-13, 2000 meeting. They are included here to present the full range of opinion and to document all edits suggested by panelists.

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Joe L. Mauderly, DVM

GENERAL COMMENTS

This revision is a substantial improvement over the last draft, and reflects a serious attempt to incorporate the comments and guidance of the CASAC panel.

Overall, I would agree to close on the document in its present general form, pending satisfactory edits by NCEA to address residual key issues and numerous lesser editorial items. The majority of my comments address editorial faults and lack of clear statements or descriptions of studies, rather than substantive issues. However, some of these "minor" problems cloud the reader's understanding of the facts. There is no reason the document can't be written well, as well as adequately portraying the current state of knowledge and coming to the correct key conclusions. Although one might avoid detailed editing in drafts, the final document will require careful examination throughout for minor, as well as major, changes.

In the final version, the figures and tables need to be inserted into their proper places in the text.

SPECIFIC COMMENTS

Chapter 1: Executive Summary

1-3, 7: This is a strange statement. Can you think of any portion of the U.S. population that is not exposed to "$PM_{2.5}$ of which DE is a part"? Why not just say that everyone is exposed?

Chapter 2: Diesel Emissions Characterization, Atmospheric Transformation, and Exposures

2-2, 35: Compression ignition is not just an example of a type of internal combustion engine in which diesel fuel is burned – it is the only type. Just eliminate the "e.g.".

2-3, 4-10: This description is confusing. In line 7, you state that DPM "are considered fresh after being emitted and undergoing aging". I don't think that's what you mean. The point is well taken that there is fresh DPM and aged DPM, but the wording of the paragraph needs some attention.

2-8, 18: It does little good to refer to the "Zeldovich mechanism" unless you explain briefly what it is, or at least give a reference. Very few readers would have heard that term before.

2-9, 8 and 29 (and elsewhere): The terminology in sections describing DPM and ambient PM need to be tightened up. DPM is a ubiquitous part of ambient PM. Of course, if you analyze pure DPM it will have a composition overlapping with, but different on average than, ambient PM. The toxicity of ambient PM samples and pure DPM may well be different. Regardless, DPM is part of ambient PM. With a little attention, the wording can be changed to more accurately explain your point. Taken to ridiculous extreme, if one listed each subset of ambient PM as different from ambient PM, there

wouldn't be any ambient PM left! The sloppy terminology tends to mislead the naive reader in thinking that DPM and ambient PM are two completely different things. The opportunity that is lost in the present wording is to provide a clear and accurate perspective that the many materials comprising ambient PM differ in nature; thus, the average composition necessarily differs from the composition of any individual component. That's not difficult to state.

2-13, 31: Shouldn't it read "and the maximum" instead of "or the maximum"?

2-22, 36: Here is the Zeldovich mechanism again. If it's worth citing twice, it's worth explaining, or at least referencing, once.

2-25, 23: If the "hydraulic-electronic unit injection" the system commonly called "common rail"? If so, since "common rail" is the more commonly-used term, it would be good to put it in parentheses in this sentence.

2-27, 6: First, has "DDEC" been defined? If not, the abbreviation is worthless. Second, write out Detroit Diesel Corporation. You don't use the abbreviation DDC consistently (eg, next page, line 30), and you write out names of other engine manufacturers.

2-28, 33-34: This sentence needs fixing. You use the term "two stroke" twice.

2-32, 4: You make the point that the sample from the tunnel could be taken as representative of heavy engine emissions, and you may be correct. However, you support that premise with two facts that are not convincing. First, 25.7% doesn't seem like a "relatively large" percentage, as stated. Relative to what? Second, the number of heavy-duty vehicles passing through the tunnel doesn't mean that the sample was predominated by those vehicles. You would have to make the case on the basis of the relative volume of emissions from heavy and light-duty vehicles, but you don't make that case directly.

2-34, 15 and 31: Here is "DDC" again.

2-41, 17: Here, you use the term "intercooled". Elsewhere you use the term "aftercooled". Neither term is defined. Are they the same?

2-42, 30: The terminology here is not clear. Do you mean a decrease in the amount of emissions, or a decrease in the range (number, type?) of "factors"?

2-44, 1: A given set of dilution tunnel conditions can model "what occurs" in the atmosphere, but only under that one condition. The point is not that dilution tunnel results can not be representative (ie, accurate), the point is that no dilution tunnel condition can accurately represent the full set of conditions, or range of conditions that occur in the environment. Without that clarification, a naïve reader would

assume that dilution tunnel results have no value, rather than understanding correctly that their value is limited to a specific set of conditions.

2-46, 34: Sentence needs to be fixed.

2-52, 6-12: There are conflicting statements here. It is stated that DPM have limited hygroscopic growth when fresh, but have more when aged. It is then stated that DPM "do not appear to undergo hygroscopic growth once emitted to the atmosphere". You can't have it both ways.

2-54, 35: Presumably, the first "PM" in the sentence should be "DPM".

2-57, 31-32: It sure doesn't. Mel Zeldin (SCAQMD) has stated in public meetings that they believe that today, only about 33% of EC in the basin is from DPM. This is a big difference from 67%. If you want to be contemporary, you might want to call Mel and include a quote here.

2-63, 21: I've heard of biomarkers for benzene exposure, but what biomarker is specific for particle-associated benzene exposure? If there isn't one, then this statement is misleading.

2-67, 12-13: This information needs clarification. If the freeway contributed 0.7 to 4.0 "excess" DPM, what does "a maximum of 7.5" mean? Is this including background? What measurement was taken as "background"?

Chapter 3: Dosimetry of Diesel Particulate Matter

3-1, 28: Bad sentence – "here" is Chapter 3, not Chapter 2. Just say they are described in Chapter 2.

3-1, 29-30: It should read "—are the focal points—".

3-2, 15: I believe that a larger range is portrayed in Chapter 2.

3-3, 25: You already defined these abbreviations above.

3-3, 33: Some agglomerated DPM are larger than 1 micron. Most are not, but the statement isn't true as it stands.

3-5, 24-25: The presentation of the issue of interspecies differences (or similarities) in deposition is confusing. The statement here, along with figure 3-1, indicates that there is no important species difference in lung deposition. First the reader has no idea what is meant by similar "relative deposition" Second, this premise conflicts with the three-fold differences in deposited dose given in Table 3-1. Are you saying that all of the interspecies difference in deposited dose is due to differences in ventilation rate? If not, then we need more explanation. If so, is that consistent with current best thinking.

3-6, 26: I think you mean "different" particles, not "specific" particles.

3-7, 34: Are you making the case that there would be no difference in clearance from either region for DPM vs. 4 micron particles? Do we know that?

3-8, 18: It was exposure of rats to whole exhaust containing DPM, not just to "whole DPM".

3-8, 24: Again, the exposure was to whole exhaust containing these concentrations of DPM. The same problem appears again in lines 36, 31, and 33.

3-9, 5: It would be more informative to state that a larger fraction of DPM translocated to the interstitium in heavily-exposed primates than in heavily-exposed rats. We really don't have information on whether the same difference might exist in animals exposed to environmental levels of DPM.

3-9, 16-18: It would be more informative to state that the reason it isn't relevant is that there were no airway tumors in the rats. The tumors were all parenchymal, so nothing that happened in the airways could have directly affected them.

3-10, 24: Did Chan expose rats to whole exhaust containing this concentration of DPM, or just to resuspended DPM, as the present wording implies?

3-11, 20: I think there should be an opening parenthesis before "CxT".

3-12, lines 19, 29, and 32: I believe that the exposures were to whole exhaust in all these cases. Same on P 3-13, 11.

3-20, lines 29, 34: Again, the exposures weren't just to DPM, they were to whole exhaust.

3-22, 18: It should be "rodents" rather than "animals". The predominant site was not alveolar macrophages in primates. I guess it might have been if you postulate that the interstitial burden was contained in "alveolar" macrophages that migrated there. Are you making that case?

3-29, 4: The sentence need fixed. "Some deposition conducting airways" doesn't make sense.

3-31, lines 6,7: So what precludes you from using a multiple-path model for deposition and some other model for clearance?

3-36, 29: Which "much larger particle" are you referring to – 0.4 or 2.0 microns?

3-37, 16: "Extimated" is a misspelling.

3-44, Table 3-2: Shouldn't the title read "—exposed to DPM in whole exhaust"? As in the text, implying that the exposures were to only DPM is misleading.

3-48, figure legend: The "3" at the end should be a superscript.

3-49, figure legend: It should be "mg DPM", not "mg PPM".

Chapter 4: Mutagenicity

4-3, 18: First, what is "tar"? This is the only place in the document that uses that term. Regardless of what the authors might have called it, you need to put the exposure material in context within the terminology used in this document. In view of the preceding sentence, you must mean "extract". Second, why cite a reference that dosed animal intraperitoneally with 2-4 g extract per kg? That would be equivalent to 140-280 g in a 70 kg human! A human wouldn't absorb that much extract in a lifetime, much less a female during a single pregnancy!

4-3, 24: Presumably the exposure was to whole exhaust, not just DPM. This is especially important when you are talking about mutagenicity, given the amount of SVOCs that go through filters.

4-4, 17: In what cells were the adducts measured?

4-5, 24: Was the exposure to whole exhaust?

Chapter 5: Noncancer Health Effects of Diesel Exhaust

Note: This chapter does a particularly good job of providing summary statements at the end of each section. The other chapters would do well to emulate this one in that regard. On the other hand, this chapter stands out as failing to mention the exposure or dose used in many of the studies cited.

5-3, 17-18: How could an increase in nasal ascorbate prevent further oxidant stress in the "respiratory tract"? Presumably, you mean only in the nose – or do you mean that you are assuming an increase in ascorbate throughout the tract?

5-6, 23: It would be better to have a separate heading for the "traffic" studies. They are really a different type of study in which "exposure" is quantitated in terms of traffic rather than any airborne material.

5-8, 4: I know I'm from the provinces, but what is an "express tunnel", and would someone be sitting in one – as the sentence implies?

5-9, 5-10, and 5-11: The doses are not stated in several of these paragraphs. Specifically, the paragraphs beginning on 5-9,11, 5-9, 34, 5-10, 26, 5-11, 9, and 5-11, 17. Without some indication of dose, the information is of limited value.

5-21, 6-8: This statement doesn't derive from the studies presented in this section. If you want to make a case for the organics (which is reasonable), then cite the studies demonstrating the relationship. If you can't cite studies, don't make the statement.

5-40, 25: What was the exposure concentration?

5-41, 16: What was the range of doses?

5-41, 21: What was the dose? Why cite studies using intraperitoneal injection when there are several studies dosing via the respiratory tract?

5-41, 30: What was the dose?

5-42, 9: What was the dose? Why cite a footpad study when we have respiratory studies?

5-42, 20 and 30; 5-44, 18 and 30; 5-45, 15 and 22: What were the doses in these studies?

5-53, 27; and 5-54, 1: What were the exposure concentrations in these studies?

5-57, 5: The wording states that pyrene adsorbed to DPM augments the adjuvant effect. That is not what the study demonstrated. What you don't say is that the only single organic compound they tried was pyrene. They used that as a model compound, and speculated that it may also act that way on DPM. While it is true that the studies showed that pyrene could have this effect, it is very misleading to imply that pyrene adsorbed to DPM causes the effect, much less is chiefly responsible for the effect. It is likely that several organic compounds could have this effect in pure form, and also a reasonable hypothesis that they do the same when attached to DPM. You do a disservice, however, by citing the study in a way that leads the reader to a misunderstanding of the facts. This whole issue is very important, and it is appropriately cited in this chapter. There is no reason to cloud the issue by not being clear about what we do and don't know at this time. It would also provide perspective to note the dose of pyrene used to achieve this effect, and how that relates to doses expected from environmental exposures.

5-59, 9: What was the dose in this study?

5-59, 29: This statement is exactly backwards. There was less aggregation in the mice, not in the rats.

5-64, 9: It should say "—lung tumors <u>in rats</u>".

5-69, 25: It would probably be more precise to use "potency" rather than "efficacy".

<u>Chapter 6: Quantitative Approaches for Estimating Human Noncancer Risks of Diesel Exhaust</u>

6-2, 21: Is "adjuvancy" really a word?

6-4, 24: Do you really mean PM_{15}, or do you mean PM_{10}?

6-11, 19-21: Is this really true? What about the Fred Miller et al. Model – isn't that one parameterized for humans and rats and currently available?
6-12, 7: Didn't you use the retained lung burden as the "dose", rather than the air concentration? An air concentration is an exposure metric, not a dose metric. I thought that the model(s) used for HEC compared species on the basis of retained PM.

6-12: It would seem that somewhere on this page, it should be made explicit that the extrapolation assumes the equivalence of CxT = CxT. That is, "dose" was adjusted across species assuming that a weekly non-continuous exposure could be extrapolated to a continuous exposure by dividing by the hourly ratio. This is a reasonable assumption under the circumstances, but is an important feature of the extrapolation. For example, this is an important assumption underlying the information given in 6-13, 17-21. The reader can catch this point from footnote b in Table 6-2, but it should be made clear in the text.

6-16, 4: You could say that some studies report, or that studies occasionally report, but you probably shouldn't say that some studies occasionally report.

6-17, 32-34: This sentence is confusing. You note that environmental exposures can be above the RfC for short times, which is true. You then say that time-averaging is not part of the assessment. In calculating the RfC, you did time average the animal exposures to estimate and equivalent continuous human exposure. All of the animal exposures were episodic, in the sense that none were continuous. Thus, an acceptance of time averaging is implicit in your method. Surely you don't think that anyone would be exposed to 14 ug/m^3 continuously for a lifetime! Overall, to say that time averaging was not part of the assessment is misleading.

6-18, Ishinishi et al. Data: You should note that the two data sets are for LD and HD. Also, why is there a space between 1.84 and 3.72 lines in the HD data set?

6-20, Table 6-2: One cannot tell from the table or the explanation why you lumped together 2.44 and 6.3 exposure levels for the Nikula 1995 study.

Chapter 7: Carcinogenicity of Diesel Exhaust

7-1, 23-25: You should note that these are estimates, or modeled data. Simple inserting "it was estimated" would suffice.

7-2, 8-9: I think you are confusing the reader here about the difference between "health risk" and "burden". The health burden for DPM can't be larger than the health burden for PM. However, the health "risk" in terms of unit risks, could be much higher for DPM than for PM. There is enough confusion on the street about this issue without contributing to it!

7-4, 15: The term "potentially exposed" is misused here. Of course the workers were exposed – everyone is. The point is that these workers had potentially much higher exposures than average.

7-7, 7: Don't you mean "positive" association instead of negative? A cancer effect would be a positive association.

7-64, 4: Imbalances in smoking prevalence are only one way smoking could be a confounder. If smoking acts synergistically with diesel exposure, then smoking could be an important confounder even if smoking was similar among exposed and control populations.

7-65, 12-13: Why not just say that Hill provided a set of criteria? Others have used the criteria, but they didn't "provide" them. The criteria that I've heard used by all during the past several years all stemmed from the Hill list.

7-67, 28: The references you list are all "rat" references. Why not say that diesel exhaust has been shown to cause cancers in rats, rather than in "animals". If you really mean to be more inclusive, add some other references.

7-132: The high concentration in the Mauderly mouse study is listed as 7.0 mg/m^3. In the text and on page 7-127, it is cited as 7.1 mg/m^3. The reported concentration was 7.08 mg/m^3, so 7.1 would be the more correct. At least be consistent.

7-139, Table 7-9: There is no "DHHS, 2000" in the reference list.

Chapter 8: Dose-Response Assessment: Carcinogenic Effects

8-1, 4: There is an "and" missing between "data" and "Discusses".

8-13, 17: Wouldn't the equivalent exposure be 21 ug/m^3 instead of 20?

8-13, 28: The point here is not clear. How are you separating on-road from non-road sources? Surely you don't mean the this entire document has only discussed risk from on-road sources. The hazards and risks described throughout the document presumably include those from diesel exhaust from all sources. How then do you propose that exposure to off-road sources confers some special risk? This doesn't make sense.

Chapter 9: Characterization of Potential Human Health Effects of Diesel Exhaust: Hazard and Dose-Response Assessments

9-3, 2: It should read "—most other ambient PM –". The present wording suggests that DPM is not part of ambient PM.

9-9, 25: It should read "—exposure to high concentrations of DE –". As for cancer, non-cancer effects have only been demonstrated in animals at high concentrations of exposure. Regardless of how you extrapolate to humans, the fact remains that animals have only demonstrated effects at high exposure levels.

9-9, 30: Presumably, you mean "—mainly from rats –". I've looked inside lots of rats and I've never seen any data in there!

9-13, 17-18: The meaning here is not clear. What do you mean by stating that the carcinogenicity appears related to particle size? Do you have data on carcinogenicity of diesel soot of different sizes that supports this premise. Regardless of what you might have meant here, the statement should be clarified. It could be taken, for example, to suggest that ultrafine DPM are more carcinogenic than "regular" DPM. We have no data suggesting that.

9-13, 22: The meaning of this statement is not clear. I presume that you must mean that the organics may have a greater "relative" importance at low exposure levels. If they have importance at all, then they would have importance at all levels. You must mean that since elemental carbon is thought to be important in the rat response at high levels, but there is no rat response at low levels, the organics could still be important in humans at low levels. That is a reasonable hypothesis, but that doesn't mean that the organics are any less important at high levels of exposure.

9-17, 25: You don't mean 0.14 ug/m^3 here, you mean 0.14 mg/m^3. It would be better to use 14 ug/m^3 to be consistent with the RfC chapter.

9-18, 21: It should read "-0- limit for DPM would be –". If you are talking about "DE", the mass concentration would be higher. I think you are just talking about DPM.

9-18, 25: Where else would DPM come from other than DE sources?

9-18, 26-29: This statement doesn't make sense. It could only apply if you some standard portion of PM was DPM. If you want to speculate about relative toxicity, this isn't the way to do it. The whole example doesn't make sense. If DPM and other ambient PM have the same toxicity, you could have DPM at any concentration up to 15 ug/m^3 and not exceed the toxic hazard of the 15 ug/m^3 annual PM standard. DPM constitutes a variable portion of PM. It may be more or less toxic than other PM. If all PM were equally toxic, you could have any mix up to a total concentration of 15 ug/m^3 and meet the intent of the annual standard. The general point that not all PM are likely to be equally toxic and that DPM may be more toxic than most is a reasonable one to make, but the present wording only confuses the issue.

9-19, 3-7: I don't agree that the apparent congruence of the RfC and the annual PM standard suggests the validity of either. I could argue equally well that the congruence suggests that one or both must be

wrong. Happening to come out with close to the same number may be reasonable and acceptable, but that certainly doesn't support the validity of either number. Remember, in the last draft you were equally convinced that the RFC should be 3 times lower. Overall, you'd better let well enough alone and not try to construct a circular argument for why the congruence imparts confidence.

9-24, 25: Just which area in the U.S. does not have ozone present? There is ambient ozone everywhere. The statement doesn't make sense. Now if you want to argue from the basis of data in hand that there is some synergism and that DPM may have greater effects as accompanying ozone exposures increase, you may have a defendable point. However, that's not what the sentence says.

Philip Hopke, PhD

Chapter 2

They have made a very comprehensive review of the information that is available on diesel emission rates, characteristics of those emissions and the amounts of diesel particles that can be estimated to be present in the ambient air. One of the problems with this chapter is that it does not provide any clear links to the health risks of diesel exhaust. It would be useful to provide some pointers to the discussions that will come later in the document. For example, given the information they provide with respect to the significant differences in railroad diesel fuel relative to highway and off-road diesel, there should be some comment about how this might affect the epidemiology of railroad workers relative to truckers.

One aspect that is still missing in either chapter 2 or possible chapter 3 is the response of diesel particles to the high humidity conditions it would encounter in the respiratory tract. One of the important characteristics of diesel particles is that they do not demonstrate significant hygroscopic growth. Hygroscopic growth has been examined by several investigators (Weingartner *et al.*, 1993; 1997; Dua *et al.*, 1999) and find that these particles do not exhibit growth. In fact, they appear to have some decrease in size with higher humidity possibly through the collapse of the fractal aggregate structure. This point has been raised in prior reviews, but has yet to be added. This raises questions about their level of understanding of particle dosimetry.

References

Dua, S.K. , P.K. Hopke and T. Raunemaa, (1999) *Water, Air, Soil Pollution* 112: 247-257.

Weingartner, E., Burtscher, H., and Baltensperger, U. (1993). J. Aerosol Sci. 24:S371-S372.

Weingartner, E., Burtscher, H., and Baltensperger, U. (1997). *Atmospheric Environ.* 31:2311-2327.

Warren H. White, PhD

Chapter 2

In the subset of tables and figures that my interests led me to examine closely, I came across several substantive errors.

Table 2-18. I can't find PAH emission rates broken out by different fuel types anywhere in Norbeck et al. (1998c), the cited reference. Moreover, the values in this table are 2 or 3 orders of magnitude higher than those given by Norbeck or those in the HAD's unsourced Table 2-18.

Table 2-25. The values given for Rochester and Washington presumably belong in the $\mu g/m^3$ column rather than the % column. The footnote symbols for MATES II and 'not available' are reversed.

Table 2-26. Anaheim has a quarter-million people, and is identified as 'urban' in Table 2-25. It is unclear that the distinction urban/nonurban has any meaning within the LA basin.

Figure 2-33. The Schauer et al. (1999) study employed TOT rather than TOR for the EC measurement. Rogge et al. (1993) employed a method different from the DRI TOR used for Zielinska et al. (1998) and Norbeck et al. (1998).

Figure 2-34. (A) The plotted values (y-axis) give EC content as percent of total fine particulate matter, not as percent of total carbon. For example, Schauer et al. (1999) report EC as 30.8% of fine particle mass and OC as 19.7% of fine particle mass, for an EC/TC ratio of 61%. (B) I can't find in Zielinska et al. (1998) the 33% EC content plotted for engine model year 1990. (C) All four data references have coauthors, not just Zielinska.

TOR vs TOT

Two different thermal-optical procedures are widely used to determine the fraction of a sample's total carbon present in the reduced, or "elemental," form. These are variously identified as the TOT/Sunset Labs/NIOSH and TOR/DRI/IMPROVE methods, and they are known to yield substantially different EC/OC splits (Countess, 1990; Chow et al., 2000; Norris et al., 2000). Both methods evolved from a common ancestor (Johnson et al., 1981) over the course of a decade or more, complicating the interpretation of trends and the integration of data from different studies, particularly those from different years. This situation will likely continue, as the Agency has invested in two large ambient monitoring networks (IMPROVE and $PM_{2.5}$ speciation), the former employing the IMPROVE method and the latter the NIOSH method.

The distinction between SOF and thermal-optical determinations of OC is noted and discussed in section 2.2.8.1.1, but the distinction between TOR and TOT determination of EC is overlooked in

section 2.2.8.1.3. Six lines in section 2.4.2.2 seem to be the only mention anywhere of this pervasive source of ambiguity. As I note in my Chapter 9 comments, failure to distinguish between TOR and TOT determinations of EC is an important source of uncertainty in estimates of ambient DPM concentrations, which are central to this assessment. Paul Solomon and other air monitoring people at EPA are actively studying the disagreement between TOR and TOT, and should be consulted on this subject.

EC as surrogate for DPM

The discussion on page 2-57, lines 23-31, uses far too many significant figures. Neither the 64% cited for EC as a fraction of DPM nor the 67% cited for the diesel share of EC differs in any meaningful way from the fraction 2/3. To claim that DPM = 1.04*EC rather than DPM j EC is absurd. (Note that 'HC' is erroneously substituted for 'EC' in line 31, and again in all three displayed equations on page 2-58.) Over-interpretation of the approximation DPM j EC continues on page 2-58, and concludes with the circular logic in lines 22-27, which overlook the fact that the surrogate calculations are themselves based on the CMB apportionments supposed to validate.

References

J.C. Chow, J.G. Watson, D. Crow, D.H. Lowenthal, and T. Merrifield (2000) Comparison of IMPROVE and NIOSH carbon measurements. Paper presented at PM2000, Charleston.

R.J. Countess (1990) Interlaboratory analyses of carbonaceous aerosol samples. *Aerosol Science & Technology 12*, 114-121.

R.L. Johnson, J.J. Shah, R.A. Cary, and J.J. Huntzicker (1981) An automated thermal-optical method for the analysis of carbonaceous aerosol. In *Atmospheric Aerosol: Source/Air Quality Relationships*, E.S. Macias and P.K. Hopke editors, American Chemical Society, Washington.

G.A. Norris, M.E. Birch, M.P. Tolocka, C.W. Lewis, P.A. Solomon, and J.B. Homolya (2000) Comparison of particulate organic and elemental carbon measurements made with the IMPROVE and NIOSH Method 5040 protocols. In existing HAD draft references.

Chapter 9

This chapter has clearly benefitted from the added round of editing and revision. I particularly like its explanations of risk-assessment concepts and Agency guidelines. At the end of the day, however, I find that I still don't understand the larger question of why the Agency needs this assessment of diesel exhaust as an air pollutant that is distinct from its chief constituents, fine particulate matter and nitrogen oxides. Is the need a statutory one? A consequence of overlapping regulatory paradigms? A response to a singular practical issue?

Given the $PM_{2.5}$ NAAQS, why should we worry specifically about diesel PM? This chapter notes as one reason that somewhat different constellations of health effects have been suggested for $PM_{2.5}$ and DPM. Another reason is that some components of $PM_{2.5}$, such as silt particles and sulfuric acid droplets, are chemically quite dissimilar to diesel exhaust particles. But one can grant that it makes sense to distinguish silt particles from engine exhaust and still question the need to distinguish between the compression- and spark-ignition contributions to engine exhaust. Are gasoline and diesel exhaust qualitatively so distinct in terms of particle composition?

Diesel PM is distinctively rich in EC; the chapter gives a range of 50%-75% for the EC fraction of DPM mass. However recent measurements also find substantial EC fractions in gasoline exhaust. Norbeck et al. (1998) found EC to contribute over 40% of PM emissions averaging 7 mg/mi from nine 1991-97 light duty gasoline vehicles in southern California. Similarly Watson et al. (1998) found EC to contribute over 40% of PM emissions from light duty gasoline vehicles during cold start operation in Denver. Diesel exhaust also contains benzene, PAHs, and other carcinogens, but again so does gasoline exhaust. Indeed, gasoline exhaust contains substantially higher proportions of the heavier PAHs such as BaP (*e.g*. Watson et al., 1998).

One could argue that diesel and gasoline exhaust are different and variable mixtures containing EC and a suite of organic toxicants in common. Given the document's characterization of risk in terms of orders of magnitude, are several-fold differences in EC content or larger differences in the relative proportions of different individual PAHs actually significant?

Ambient exposures to DPM

The document often interprets EC as a marker for diesel exhaust, but large ambiguities in its measurement continue to confound the Agency and the scientific community. There are currently two different analytic methods for distinguishing EC from OC, variously identified as the TOT/Sunset Labs/NIOSH and TOR/DRI/IMPROVE methods, and they are known to yield substantially different EC/OC splits (Chow et al., 2000). (Note in Figure 2-34, for example, that the sole post-1990 DPM sample showing less than 50% EC (Schauer et al., 1999) is also the only one analyzed by TOT rather than TOR.*) Both methods evolved from a common ancestor (Johnson et al., 1981) over the course of two decades, complicating the interpretation of trends and the integration of data from different studies. This situation will likely continue, as the Agency has invested in two large ambient monitoring networks (IMPROVE and $PM_{2.5}$ speciation), one employing each method. It presents an overarching problem for the Agency, and this chapter of this document presents a good opportunity to highlight its generic importance.

Additional ambiguity in reports of EC as a fraction of total carbon is introduced by the OC measurement, which is sensitive to sampling conditions. Schauer et al. (1999), for example, found 35% less OC in their DPM when they sampled behind an XAD denuder to remove organics in the gas phase.

* [The caption of Figure 2-33, which claims that all studies employed TOR, is incorrect (Schauer et al., 1999, page 1579). The vertical axis of Figure 2-34 is also incorrectly labeled: the plotted EC values represent % of total particle mass, not % of total carbon.]

This document (and individual investigators) sometimes combine EC values from different data sources without accounting for their origin in different measurement methods. Given the similarity of EC contents in some gasoline PM to those in DPM, such combining of inconsistent source and ambient EC measurements has the potential to yield sizeable errors in estimates of DPM exposures. I would accordingly direct more emphasis on page 9-6 to the fact that all DPM concentrations in the middle paragraph represent uncertain estimates rather than actual measurements.

Human evidence for carcinogenic effects

This is a charged subject, in which a single line of 'spin' can squander the credibility purchased with a paragraph of balanced discussion. There are a couple of points where the Agency seems to be reaching.

9-11, 8+: *"Although some studies did not have information on smoking,* ***confounding by smoking is unlikely because the comparison populations were from the same socioeconomic class****."*

Is socioeconomic class such an accurate predictor of smoking? How fine a class structure are we talking about here? The previous draft (11/5/99) was more cautious on this point, concluding that (7-81, 11+) ".. a possibility remains that the statistical adjustment for smoking is not completely effective, and residual confounding by smoking may persist to bias the measure of the diesel exhaust-lung cancer association."

9-15, 8+: *"..examination of the available PM data has not resulted in the identification of a cancer hazard for ambient PM, although* ***there is some evidence indicating a possible association between ambient PM and lung cancer.****"*

'Some evidence' consists of three familiar studies (pages 7-2,3,4). The first is Six Cities, which reported a non-significant RR = 1.37 for lung cancer. The HEI reanalysis (Krewski et al., 2000) found this association, unlike those for all-cause and cardiopulmonary mortality, to disappear when he accounted for occupational exposure. The second is the ACS study, which reported a significant RR = 1.36 for sulfates, but no association with fine particles. It takes considerable effort to construe these results as linking cancer with the carbonaceous DPM that is elsewhere the focus of this document. The final exhibit is the AHSMOG study, which I previously understood to have found no significant associations between pollution and mortality. I now learn that recent analyses show a cigarette-like RR = 23 for lung cancer in nonsmokers from PM_{10}; unfortunately, the citations given for this stunning finding are missing from the list of references. Please! One can as reasonably assert that there is 'some evidence' indicating a possible association between air freshener and lung cancer.

Relationship between risks from DPM and ambient $PM_{2.5}$

I appreciate the Agency's attempt to accommodate the Committee's previous recommendation that it acknowledge the connection between DPM and $PM_{2.5}$. After reading sections 9.5.1.2-4 I also appreciate its previous lack of enthusiasm for the task, as the resulting discussion has a distinctly Alice-in-Wonderland flavor. Risk analysis is the Agency's mission, however, and the Agency should be able to articulate its logic more persuasively than it has in the following passages.

9-18, 18+: *"If one assumes that the adverse health effects of ambient fine particles are due entirely to DPM, ... the upper-limit for DE would be 15 lg/m^3."*

But if DPM is "typically in the range of 10%" of $PM_{2.5}$ mass (line 26), $PM_{2.5}$ epidemiology then implies that 15 lg/m^3 DPM is associated with the (rather severe) health risks observed at 150 lg/m^3 $PM_{2.5}$. That is, if DPM is "exceptionally toxic" then we need DPM < 1.5 lg/m^3 to obtain the protection associated with the $PM_{2.5}$ NAAQS.

9-18, 26+: *"If one assumes that DPM is as toxic as other constituents of ambient $PM_{2.5}$, then ambient concentration to* [sic] *DPM needs to be below the range of 1.5 to 5 lg/m^3 ... to achieve the same protection for the annual average standard for ambient fine particles of 15 lg/m^3."*

By this same logic, if 1.5 lg/m^3 is an acceptable lifetime exposure level for DPM, then it is <u>not</u> an acceptable level for either on-road DPM or off-road DPM. And if, say, 1 lg/m^3 is an acceptable lifetime exposure level for the on-road portion, then it is not an acceptable level for diesel busses. And if .... etc. Alternatively, if back-yard barbeque smoke (the Chamber of Commerce's favorite pollutant) is as potent as DPM and one-tenth as abundant in urban air, then back-yard barbeque smoke needs to be below 0.15 lg/m^3 to achieve the same protection. Does the Agency really want to place itself in the position of having to choose between barbeques and public health?

9-19, 5+: *"This congruence of independent methods should also increase overall confidence in these estimates .."*

Two of the three methods are hardly independent, resting directly on the $PM_{2.5}$ NAAQS. Their agreement (to within an order of magnitude) is a simple consequence of the agreement between ambient DPM and $PM_{2.5}$ concentrations (to within an order of magnitude).

Miscellaneous details and typos

9-2, 27+: Hasn't 'microns' become politically incorrect? Aren't we now supposed to say 'micrometers'?

9-3, 7: It's a fact, not just an expectation, that 'Some geographic areas have a higher percentage of DPM in $PM_{2.5}$.' Period.

9-3, 9: The 1982 estimates cited here are all for different sites in the same urban California region, greater Los Angeles.

9-3, 18: How can 'some DPM organic constituents' be higher than the upper limit of the range for the 'organic carbon portion of DPM'?

9-13, 22: I think the author means to say that the relative importance of adsorbed organics may increase at lower exposure levels.

9-17, 25: The NOAEL is 0.14 milligrams per cubic meter, not micrograms.

9-19, 18: According to the destinction drawn at the top of page 9-13, I think the author means 'mode(s)' rather than 'mechanism(s)' here.

9-20, 12: 'DE' should modify 'exposure' rather than 'workers'.

Additional references

R.L. Johnson, J.J. Shah, R.A. Cary, and J.J. Huntzicker (1981) An automated thermal-optical method for the analysis of carbonaceous aerosol. In Atmospheric Aerosol: Source/Air Quality Relationships, E.S. Macias and P.K. Hopke editors, American Chemical Society, Washington.

D. Krewski, R.T. Burnett, M.S. Goldberg, K. Hoover, J. Siemiatycki, M. Jerrett, M. Abrahamowicz, and W.H. White (2000) Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of particulate air pollution and Mortality. Health Effects Institute, Cambridge.

J.C. Chow, J.G. Watson, D. Crow, D.H. Lowenthal, and T. Merrifield (2000) Comparison of IMPROVE and NIOSH carbon measurements. Paper presented at PM2000, Charleston.

Arthur Upton, MD

Chapter 4

The revisions that have been made in Chapter 4 respond effectively to the following criticisms which were leveled against the preceding draft: 1) this version of the report contains an appropriately expanded discussion of current information on the mutagenicity of particles having little or no organic content, including evidence for the involvement of reactive oxygen species as demonstrated by the work of Driscoll and others; 2) this version also includes a discussion of the mutagenicity of oxygen radicals, which are thought to contribute to the tumoigenic effects of chronic high-level exposure to diesel exhaust particles on the rat lung; and 3) this version cites the work of Wallace, Keane, et al. at NIOSH on the mutagenic activity of whole DPM, as was recommended.

This version of the report does not adequately respond, however, to the criticism that it should place the high does used in mutagenicity assays in context relative to the does likely to occur from inhalation.

As concerns editorial issues, the statement on page 4-4, line 24 that "both adduct and mutagenicity were highest among the 16 most exposed" is confusing in that it appears to contradict the preceding sentence, which states that hrpt mutant frequencies in workers did not differ from those in controls.

Pages 6-2 to 6-6: in addition to the references cited, the document should cite the newly published article by Daniels, Dominici, Samet, and Zeger (Am. J. Epidemiol. 152: 397-406, 2000), which reports that the data for the 20 largest U.S. cities are best fitted by a linear-nonthreshold relationship between PM10 and daily mortality from all causes and from cardiorespiratory causes; and which concludes that "linear models without a threshold are appropriate for assessing the effects of particulate air pollution even at current levels".

Pages 6-6 to 6-7 and page 6-21: if daily mortality may vary as a linear-nonthreshold function of particulate air pollution, ought it not to be included among the non-cancer health risks considered in this chapter?

Page 7-114, line 25: the statement here and elsewhere (e.g., page 8-3, line 13, and page 9-15, line 1) in the document that "the mode of action for DE-induced lung tumors in rats is sufficiently understood" is not scientifically justified. I would suggest another wording; e.g., "Although the mode of action by which DE may pose a risk of lung cancer for humans is not fully known, the tumor-inducing action of DE on the rat lung appears to depend on particle overloading of the lung and is therefore judged to be irrelevant for purposes of assessing the risks of ambient levels of DE, as discussed in Section 7.4".

Page 8-14, line 7: since DE is not known with certainty to be a carcinogen for humans, the statement should be reworded to read: "...pose a lifetime cancer risk ranging from a lower limit of zero to an upper limit of 10-5 to 10-3".

Page 9-9, Section 9.4.2: shouldn't daily mortality be included here, or at least mentioned?

Page 9-14, line 13: "its" should be changed to "the relevant".

Page 9-14, line 15: "appears to" should be changed to "may".

Sverre Vedal, MD

Chapter 7. Carcinogenicity.

Hill criteria

The application of the Hill criteria (pp. 65-68) for assessing the likelihood of causation is improved in this version of the document. It should be appreciated that modern views on the usefulness of the Hill criteria, such as those expressed by Rothman as referenced in the document, have significantly limited the usefulness of the criteria for this purpose. In brief, the general point of these views is that none of the Hill criteria, except for temporality, need to be satisfied by an association that is, in fact, a causal association. That is, none are necessary. Specifically, neither a strong association, specificity of effect, dose-response, plausibility nor consistency are required. One wonders about the utility of applying the Hill criteria when so little is gained by their use. Regarding the strength of an association, in the document it is noted that the strength of the association is "modest to weak". Although some studies observe relative risks of 2.0 or greater, the overall estimate across studies is approximately 1.3 to 1.4, which I would argue is a weak association. The Hill criteria that are probably met are the consistency criterion and the biological plausibility criterion. It is not clear that the dose-response criterion is met. Specificity is partially met, although studies have either not addressed other effects or have lacked power to do so. The temporality criterion is assumed and not tested. The conclusion based on the discussion of the Hill criteria, and as repeated in the Weight of Evidence section (p. 110), seems forced. I would recommend basing arguments for causality, when using the epidemiological data, not on the Hill criteria, but rather on those characteristics of studies that determine validity.

Latency

Latency was discussed under the Hill heading of "temporality", which is only partly stretching the intent of this criterion. Nevertheless, latency is seldom directly addressed for any of the studies except in Table 7-1 where it is noted that "no latency analyses" were performed for some of the studies. Given the relatively recent use of diesel with respect to end of the follow-up period in most of the epidemiological studies, there is a sense that latency is short. Explicit assessment of latency for each study should have been attempted in the document, noting those studies where it was not possible to address the issue because of lack of information. At issue here, obviously, is whether the observed effects with the present latency periods are implausible, and therefore whether the effects observed are due to uncontrolled confounding.

In order for investigators to address latency in a more satisfactory manner, it would be interesting to perform analyses in which latency is explicitly examined. For example, one could restrict the study to include only subjects with latency of less than 10 years, in which case if similar effects were observed, one would argue that diesel exposure was not likely responsible. This would also weaken the Hill "temporality" criterion. Other strata of latency could also be examined, realizing that latency,

age, and duration of exposure would likely be correlated. Assessing duration of exposure, as a measure of “dose”, is not the same as assessing latency

PM studies

It is relevant to include descriptions of the observational studies of PM in this chapter, as was done in this version of the document. The PM "cohort" studies that included lung cancer mortality as an outcome (the 6-Cities Study, the ACS Study, and the AHSMOG Study) resulted in some interesting, but ultimately puzzling, findings. In the 6-Cities Study, deaths due to lung cancer were increased in the most polluted relative to the least polluted city, although the association was not statistically significant. The number of lung cancer deaths was not reported. In the ACS Study, lung cancer deaths increased with increasing sulfate concentrations in men, but were not increased with increasing $PM_{2.5}$ in the subset of cities with data on $PM_{2.5}$. Although the number of lung cancer deaths was not reported, they were likely 300 times larger in the ACS Study than in the 6-Cities Study, based on the relative number of deaths in the two studies. In the AHSMOG Study, with 20 female and 16 male lung cancer deaths in this nonsmoking population, ozone, SO_2 and PM_{10} were associated with lung cancer deaths in men, while SO_2 and PM_{10} were associated in women. At this time, the validity of the findings of these studies with respect to lung cancer is questionable, as is therefore their relevance to diesel carcinogenicity. A more critical review of these findings would be welcomed. Nevertheless, the final statement (p.4 , line) places these studies in reasonable perspective. However, it is not clear how this reasonable statement follows from the description of the "cohort" studies. Also on p.4 (line 5), why is the ACS finding with respect to $PM_{2.5}$, which is a negative finding, consistent with the findings of the 6-Cities Study?

Minor comments and editorial issues:

page

2 In paragraph 2, why do the PM estimates represent an "upper limit" for estimates of DPM if DPM is only part of the PM mix? That is, say if the rest of PM has no carcinogenic effects, it would be counterintuitive to conclude that any observed effects of PM would be an upper limit on effects of DPM. I may be misinterpreting what is meant, and if so, some clarification is needed (see also comments for chapter 6).

Also in this paragraph, mention is made of evidence from the cohort studies that these provide evidence on chronic effects. I am not sure they provide any evidence on chronic vs. acute effects.

50 The second paragraph is reproduced verbatim on p. 51. Although possible, please review.

52 "tskas" line 20

54 The last sentence of this page needs rewording to clarify (double negative, etc.)

60 The meaning of sentence beginning line 4 is not clear.

64 It is not clear how insufficient latency would result in increased RRs (line33).

67 Do the Garshick and Steenland studies really have adequate latency (line 6)? In chapter 8 it is noted that adequacy of the latency period is a problem for both.

99 In the last paragraph, it is argued that human lungs (and mouse lungs?) could be more sensitive to the carcinogenic effects of PAHs than rat lungs, since only in human and mouse lungs do many lung cancers exhibit mutations of p53 and K-ras genes. However, the high dose DPE inhalation studies show that in fact rats are relatively sensitive and mice relatively insensitive. This paragraph needs clarification.

10 1Section 7.4.2, as noted, refers only to particle overload conditions. It should be emphasized that the inflammatory mechanisms are largely relevant only in this setting.

106 Line 7 "increasing" is confusing, since the effects occur with decreasing particle size.

110 My reading of the application of the Hill criteria section beginning on p. 65 is that they add little to a conviction for the causality of diesel exhaust.

112 Is "limited" on line 23 too strong an adjective?

133 Table 7-4 needs a source attribution (Dasenbrock, 1996).

In the Weight of Evidence section, reference is again made to the chronic exposure rat data, which should not be used to argue for causality.

Chapter 8. Dose-response assessment: carcinogenic effects.

This chapter is generally well done. The estimates of lifetime risk based on the human observational data, of course, assume that the estimated effects are valid, that is, are unconfounded. At the very least, a qualifier to this discussion should be added, since otherwise we would be concluding that DE is a definite carcinogen, and we are merely trying to quantify the dose-response relationship. It seems unlikely that cigarette smoking is the unifying confounder. However, the relatively short latency remains worrisome, suggesting either that the effects would be stronger with an adequate latency period, or that the effects are confounded and have no relationship to latency. This latter issue raises the concern that relative risks are in fact 1.0, which would clearly invalidate the range of estimated effects that was proposed. This is related to the issue that exposure in these studies is not "diesel exhaust" but rather employment category.

Based on these reservations regarding the validity of the effect estimates in the occupational cohorts, and even legitimate concerns that the estimates may in fact be 1.0, I would not be in favor of a

quantification of risk that ranges from 1 x 10^{-5} to 1 x 10^{-3}. If such a quantification of risk is deemed important, I would recommend using the range zero to 1 x 10^{-3}. Future work should include addressing effects in cohorts with clearly inadequate latency to determine if estimated effects remain elevated, and hence not attributable to diesel exposure. If effects are not elevated for subjects with clearly inadequate latency, and adequate latency has been shown for other studies, then I would be much more comfortable with the validity of the occupational cohort effect estimates.

It was my understanding that another significant activity that is underway (first paragraph, p.11) is an extension of the period of follow-up for the Garshick cohort study, an activity which has the potential of addressing the latency issue.

With respect to cigarette smoking, on page 4 (line 16) it is noted that adequate smoking adjustment could have significant impacts on the estimates of effect, which is true. Nevertheless, when this has in fact been done, the impacts are small. Also, it is stated (line 21) that traditional statistical analyses are unable to adjust for the possibility that smokers may be more susceptible to DE effects (a notion regarding susceptibility, by the way, which if maintained should be justified somewhat better). However, this can be handled easily in a logistic regression, and in many other types of analysis, through introduction of interaction terms (between smoking and DE exposure) in the models, assuming that smoking status is known. This point therefore needs clarification.

Also regarding smoking, the sentence beginning on line 22 notes that control for smoking is a greater problem for case-control than for cohort studies because most lung cancer cases are also smokers. However, the same is true for lung cancers detected in a cohort study. That is therefore not the reason that smoking might be more difficult to control in a case-control study. A prospective cohort study is generally preferable to a case-control study since good smoking data, and data on other potential confounders, are easier to obtain, and the adequacy of the control group is not an issue. The point regarding data on confounders cannot be maintained for a retrospective cohort study such as those that address the DE issue.

Minor comments and editorial issues:

page

2 Should be “causal” (line 27)

The use of the high concentration animal data to motivate causation should be dropped.
7Add “and risk of lung cancer.” to line18 to follow “exposure...”.

Chapter 5. Non-cancer health effects of diesel exhaust.

page

2 The claim (line 2) that there have been "no well-controlled chamber" studies is out of date. The two Salvi papers referenced on p.7, and now the Nightingale study reported in Am J Respir Crit Care Med in 2000, are examples of such studies.

6 The description of the "roadway" studies (beginning line23) is one-sided in the sense that no negative studies are included. Some studies show no association with asthma prevalence, although there may be associations with asthma exacerbation.

64 The claim beginning on line 6 concluding that the "principal noncancerous health hazard to humans posed by exposure to DE is a structural or functional injury to the lung" is debatable given the, in my opinion, more compelling data in both humans and animals on the effects of DE on allergic responses.

70 Regarding the Conclusions, in keeping with my observation above on allergic effects, these effects seem more significant than either of those described in the other two conclusions: that noting increases in symptoms (an inconsistent finding) and that on chronic effects in humans and animals. Also, given the weight placed on both inflammation and fibrosis resulting from chronic exposures in the RfC in Chapter 6, the third conclusion (p.71) should include fibrosis as an important effect in the animal studies.

Reference to the Ishinishi (1988) study should be made in a consistent fashion in this chapter and chapter 6. This reference is critical to the NOAEL in chapter 6, but it is referred to as the "Research Committee for HERP Studies" (1988) in chapter 5 (Table 5-6, for example).

Minor comments and editorial issues:

page

65 line 15, "incidents" should be "incidence"

66 The two sentences beginning on line30, taken together, are confusing. The first notes that short-term DPM exposures have no apparent health effects, whereas the second details effects on the lung at "lower levels of DE". Which is it? Maybe the meaning is that these latter responses are not really health effects. Nevertheless, clarification is needed.

Chapter 6. Quantitative approaches to estimating human non-cancer health risks of diesel exhaust.

As noted in my comments on chapter 5, the animal data on effects of chronic exposure are not as compelling as the human and animal data on allergic responses. The use of the animal data on effects of chronic exposures for calculating an RfC does not therefore make use of the best data for estimating a reference concentration for DE. The motivation for not using these allergy data is that they "are

considered inadequate for dose-response evaluation" (p.9 line 16). But, as noted below, absence of dose-response information does not preclude a study from providing useful information for determining a reference concentration.

With respect to the chronic animal studies, ignoring studies that do not provide information on dose-response (for example, p.10, line 31) ignores valuable information in deriving an RfC. Even a study that made use of only one DPM concentration, since effects at that concentration are either consistent or inconsistent with the observations from studies that included a dose-response evaluation, would seem to be relevant to the RfC derivation. For example, should a study that observed no effects at the one concentration evaluated, if that concentration, say, were above the NOAEL observed in studies assessing dose-response, not be considered relevant?

It should be emphasized that we have a relatively high degree of confidence in the RfC, given that what we are highly confident of with an RfC is that the effects of concern do not occur at concentrations lower than the RfC. The EPA has gone to great pains in the incorporation of the uncertainty factors to ensure this type of confidence. This is not to suggest that effects are likely to occur at concentrations even several fold higher than the RfC, since there is no upper bound. That is, the RfC could be a gross underestimate, but higher RfCs would not give us the same degree of confidence that effects do not occur at concentrations lower than these RfCs.

Minor comments and editorial issues:
page

1 The reference to "upper limit" (line 30) here is confusing. The point being made, I believe, is that observed PM effects are the upper limit of effects attributable to DPM. As noted, DPM comprises only a fraction of PM. If DPM is more toxic than other components of PM (unlikely, but possible), the observed effects of PM would not represent an upper limit of DPM effects. Any point intended here needs to be clarified.

4 Line 22. The effect estimates in the 6-Cities study are weak, not large. Estimated public health impact should not be confused with strength of association.

16 The point regarding "congruence of estimates" is ingenuous, but is now moot based on the discussions at the CASAC meeting.

The reference to the Ishinishi study (1988) should be made in a consistent manner in this chapter and in chapter 5.

Chapter 9. Characterization of potential human health effects of diesel exhaust: hazard and dose-response assessments.

page

11 Again, the use of the Hill criteria argument (line 12) is not a very compelling one regarding a causal association in the case of DE.

12 The use of the rat data here (line13) is puzzling. The data are not useful for dose-response analysis because of the overload argument. But because this mechanism is felt, with justification, not to play a role in possible cancer pathogenesis in humans, it seems also that the data should not be used to support the presence of a cancer hazard in humans.

19 Line 3. The point about "congruence of estimates" here (and p. 22, line28) is ingenuous. It is difficult to be reassured about the reasonableness of the RfC based on the $PM_{2.5}$ annual standard when the RfC is heavily influenced by an uncertainty factor of 10 (one order of magnitude). Further, the DPM component of the $PM_{2.5}$ standard is approximately 10%, or 1.5 ug/m^3, rather than 15 ug/m^3.

Line 16. The rat data are used again.

Minor comments and editorial issues:

page

5 DPM should be PM, I believe.

14 Line 33. I would add "...and other potential confounders..." after "...the effects of smoking...". Similarly for chapter 1, p.4, line 22.

16 Line 28 (and p. 18, line 20): see discussion on "upper bound" in chapter 6 comments (reference to p.1).

23 Line 30. It is unclear what "this assessment" refers to. It seems to refer to the RfC, in which case an uncertainty factor of 10 to account for susceptible subgroups has already been incorporated. This therefore does not assume that it applies to "average health adults". This point also applies to chapter 1 (p.6, line 4).

Chapter 1. Executive summary.

See comments for chapter 9 referring to p. 6, line 4, and p. 4, line 22..

David Diaz-Sanchez, PhD

General comments

As with each new draft, I believe this is a further improvement from the previous one and is a better representation of the health risks of diesel. I believe that the more cautious approach taken in this draft towards making overstatements on both carcinogenic and non-cancer effects is warranted until more quantitative studies are published.

Chapter 5

Despite the limitations cited below I think this chapter is satisfactory with minor editing.

The agency should be commended in amplifying the number and range of articles on non-cancer effects of diesel exhaust. Indeed I believe that they have been overzealous in achieving this aim. Thus, while the study by Brunekreef et al. (2000) cited on Page 5-7, 5 is interesting and potentially very important, it should be noted that it has yet to be peer-reviewed. Similarly, Madden et al., is listed under the references as "submitted".

Despite the breadth of the articles cited there seems again to be little depth in understanding the significance of these results. For example: what is the significance of a change in IgE or goblet cell hyperplasia or mast cell influx or cytokine changes in animal models? Without a statement that these are key changes and markers of asthma, the reader is left with the impression that diesel induces a variety of immunological changes but has no idea what relevance this has to health effects.

Unfortunately, this lack of understanding leads to incorrect conclusions such as that on 5-45, 30 that "diesel exhaust has minimal effects on the immune status of rats and guinea pigs" while it does have an effect in mice. This implies that there is inter-species variation, however, as stated in the comments to the last draft report, the lack of response seen in the studies done on rats and guinea pigs (Dziedzic 1981, Mentnech 1984, Bice 1985) are to be expected since they were only performed in the absence of an allergen unlike those done on mice where an allergen (ovalbumin, house dust mite, pollen etc.) was used.

The organization of this chapter appears arbitrary. For example why is Yang et al., (1997) placed under acute exposure when this is an in vitro assay? Similarly, why are the studies by Terada et al (1997 and 1999) performed on human cells in the Laboratory Animal section (5.1.2.3.6) and not the "Human cell culture studies" section (5.1.1.1.4)? Why is Takano et al (1997) under acute exposure, when all other instillation experiments are under 5.1.2.3.6? Why are studies by Rudell et al., in a separate section than those by Salvi et al., when these exposures were performed by the same group under the same conditions and measured similar or related outcomes.

5-57,5 "notably pyrene" implies that pyrene is more active than other constituents in the organic matter, this is probably an over-interpretation. Pyrene is used in the studies cited (Suzuki et al. 1993, 1996.) as a model chemical and is not compared to others. It should be noted in vitro studies suggest that phenanthrene, benzo (a) pyrene and TCDD can affect immunogenicity and allergenicity. It may also be of relevance to note that other combustion material such as fly ash and second-hand smoke has been shown to have similar adjuvant effects as DPM in animal models.

5-40, 23 should read IgG1 not Ig1

Chapter 6

Despite the fact that almost 2/3 of articles published in the last 10 years on the non-cancer effects of diesel have dealt with immunological changes, and that acute exposures may be of more relevance than lifetime exposures, I agree with the authors that the lack of dose-response information makes taking a quantitative approach using these criterion premature. I applaud the authors for including a guidance value for DPM by treating it as a subset of total PM2.5. This is a necessity given the health outcome studies and previous statements in the documents such as 5-63, 5 "diesel exhaust toxicity results from a mechanism that is analogous to that of other relatively inert particles". The inclusion of Appendices B and C are most useful.

6-6, 22 states that DPM is typically in the range of 10%, while the executive summary (1-2, 7) gives the figure as 6%. There should be consistency throughout the document.

6-14,12 suggests that children have a greater susceptibility to DPM but 5-59,21 states that there is no evidence that the youth of an individual enhances the risk. A similar argument and contradiction is made for pre-existing conditions such as emphysema.

6-6,23 states that large numbers of ultrafine particles may make DPM disproportionately toxic. If the authors are going to make such a sweeping statement they should provide references or refer back to other parts of the document.

Eric Garshick, MD, MOH

Chapter 1: Executive Summary

General comments: This chapter needs to be rewritten to reflect the changes that will be made in the rest of the document in response to the comments of CASAC. In order to prevent confusion regarding what is known about diesel exhaust inhalation as a potential hazard (a great deal of information) with the true risk of an adverse health effect at environmental levels (very little information), these terms need to be carefully defined, and the definitions should be repeated in he executive summary and in key chapters. Differentiation between ambient cancer hazard and defining ambient cancer risk is made on the top of page 1-5, but I would consider noting this earlier in this section.

Page 1-4, line 15-17: One might extend the title of this section to "Carcinogenic Effects – Hazard Identification".

Consider ending the sentence after "inhalation" with a period instead of saying "at any exposure condition" since the phrase "at any exposure condition" is qualified in the next paragraphs. I am concerned that the uncertainties regarding the phrase "at any exposure condition" is not accurately conveyed. It is worth noting that accurate exposure-response information, particularly at low levels of exposure is not available.

Consider these sentences: " The studies on which this is based comes from epidemiologic studies of workers with occupational exposure to diesel exhaust. Although in some cases there is overlap between occupational and environmental exposures, it is not possible to establish a link between a specific exposure level and lung cancer risk with confidence and therefore determine the magnitude of the risk that occurs at specific environmental levels'. The point of this paragraph is to state that there is uncertainty about the level of risk that occurs at a given level of exposure. Although it is agency policy to consider that there is a risk at environmental levels, it is not possible to state the magnitude of risk that occurs.

Page 1-4, line 33-34: Consider this change: "hazard extends to ambient environmental levels" to "some hazard extends to environmental levels". I do not think it is necessary to include the word ambient and environmental in the same sentence.

Page 1-4, line 36: change "it is prudent public health policy to presume a cancer hazard for DE at any exposure" to "it is prudent public health policy to presume a cancer hazard for DE at low levels of exposure, although it is not possible to determine the magnitude of the risk." I am concerned the sentences as written will be taken out of context.

Page 1-5, lines 12-19: consider adding to this section "The range of the actual risk may approach and include zero"

Page 1-5, Sources of Uncertainties: This is a good section and can be referred to at the beginning of the Executive Summary so that persons do not forget the limitations inherent in the interpretation of these data.

Chapter 3: Dosimetry Of Diesel Particulate Matter

Page 3-20, line 18: Comments on the section entitled "Relevance to Humans": Consider expanding this paragraph to describe the relevance of the rat model to the occurrence of non-cancer health effects in humans. This seems important because the rat model was abandoned for both hazard identification and formal risk assessment for lung cancer, but is used to estimate an RfC value for non-cancer health effects.

Chapter 5: Noncancer Health Effects

This chapter is much improved, but there are still some points that need to be clarified. It is important to be precise when relating the relevance of experimental data to potential mechanisms of human disease. At times results are generalized and their relevance is overstated. Some the health effects attributable to PM alone Add: PM document to support some of non-cancer health effects in a qualitative sense.

Page 5-4, lines 23-24: The results summarized by the sentence "Miners with a history of smoking had an increased number of decrements over the shift than non-smokers did" needs to be restated since it is not clear what an "increased number of decrements" refers to. Presumably it refers to a greater decrement in pulmonary function over a work shift observed in smokers compared to non-smokers.

Page 5-6, line 35: Presumably truck traffic counts were associated with a decrement in lung function in these children. A stronger point can be made, rather than saying just "lung function was associated with truck traffic density". Relate roadway studies to potential diesel exposure.

Page 5-7, line 1: A sentence could be added to describe what is meant by "black smoke" in this study and how it relates to diesel exhaust.

Page 5-12, lines 4-6: These lines state that DPM has the potential to cause inflammatory and immunological responses typical of asthma. Taken at face value, this statement implies that DPM can cause clinical asthma in humans, which is a syndrome characterized by airway inflammation, bronchial hyperreactivity, and recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, as well as airway inflammation. Evidence has not been produced in humans that diesel exhaust exposure results in asthma, and I am concerned that these sentences may be taken out of context. It seems more appropriate to be more circumspect regarding the evidence for a link between the inhalation of DPM and asthma in humans.

The controlled inhalation experiments in humans summarized in the chapter document increased numbers of polymorphonuclear lymphocytes in BAL samples, the expression of the genes than result in the production of IL-8 and IL-5 (inflammatory mediators), and bronchial biopsies with an increase in neutrophils, mast cells, and lymphocytes. Nasal lavage studies reveal that DPM can act as an adjuvant to stimulate specific IgE responses and can result in the production of various inflammatory mediators in the nasal lavage cells. Therefore, a more precise way to summarize these data obtained from studies in humans and from using human cells may be that DPM can cause an increase in markers of inflammation in the nose and airway, and that some of these markers of inflammation are also observed in asthma.

The study that described the 3 cases of asthma following high dose exposure to diesel exhaust has been taken out of the section on "Immunological Effects" but would be worth noting in the section called "Short-term Exposures" since the mechanism was due to the short term inhalation of high concentrations of exhaust rather than an immunologic mechanism. The study is still listed in Table 5-1 but is not described in the text.

Page 5-12, line 8: The words "increase their effectiveness" appears at the end of the sentence. It is not clear what "effectiveness" means here. Presumably it means the effects of DPM in enhancing the IgE response, but in this left to the reader's imagination.

Page 5-61, line 10-15: This sentence regarding susceptibility to inhaled particles is not supported by data that is presented in this document. In fact, two experimental studies did not support the increased susceptibility of developing lungs or emphysema studied in rat lungs. The results of these experiments are dismissed as irrelevant to human exposure.

Page 5-66, lines 2-3: I'm not sure what the phase "doubling of a minor restrictive airway disease" means. This needs to be explained since airway disease does not typically result in a restrictive ventilatory defect.

Page 5-66, lines 20-22: This should be restated to say that DPM appears to have the potential to induce airway inflammation in humans without disease, and in one exposure study, peripheral blood changes were noted. The sentence as written does not seem to accurately capture the experimental evidence noted from human studies. How is pulmonary inflammation different from airway inflammation here?

Chapter 6: Quantitative Approaches to Estimating Human Noncancer Health Risks of Diesel Exhaust

This chapter is more clearly written than in the past and the discussion about the PM standards and health effects enhances the rationale for the development of the RfC. The message that I take from the chapter as it was originally written is that a range of possible RfC values are suggested, ranging from 15 $\mu g/m^{3\ based}$ on the PM standard, a value of 14 $\mu g/m^3$ based on animal data extrapolated to humans,

and a possible value of 1.5 µg/m^3 to 5 µg/m^3. However, it is not possible to endorse the lower values over the higher values because of the uncertainty of the data used to obtain these values. It also would be reasonable to talk about the relevance of the rat data for the derivation of the RfC to contrast this decision with the same rat data that has been rejected to for the assessment of carcinogenicity. I agree that data based on allergy may be the basis of future standards.

Page 6-14, lines 8-11: This sentence regarding persons who may be more susceptible to diesel exhaust seems speculative, and should be justified.

Line 25, page 6-16: It is not clear what is meant by "The toxicological database for DE is relatively complete". There seems to be much uncertainty regarding many questions.

It is reasonable to add the uncertainty factor of 3 to the calculation of the RfC as discussed at the meeting.

Chapter 7: Carcinogenicity of Diesel Exhaust

Overall, this chapter is more clearly written than previous versions and an improvement. Enhanced by discussion of studies of PM and lung cancer. Agree with bottom line

Page 7-3, lines 28-29: Relative risks quoted seem large here. The overall whereas the odds ratios for the long haul drivers was 1.31 (95% CI=0.81-2.11), and for the short haul drivers was 1.27 (0.83-1.93). The long haul drivers drove mainly diesel trucks, whereas the short haul drivers drove gas-powered trucks. The similarity in odds ratios and exposure levels between the short haul and long haul drivers suggests that much of the driver's exposures come from the roadway. Other issue is one of latency, and knowing for sure the types of truck driven and for how long, given that the deaths were collected 1982-83. This doesn't negate observations that diesel particles have the potential to cause lung cancer, but raises the issue that workers who work as professional drivers are exposed to particles of a variety of combustion sources.

Page 7-39, lines 9 and 10: The sentence "As far as qualitative risk assessment is concerned, this study is still considered to be positive and strong" is confusing since the quantitative risk assessment performed is not used in assessing risk in the document (due to limitations of the exposure data), and the study has already been described in the previous section. This paper doesn't add any independent information to the discussion of the previous paper.

Page 7-63, line 7: A statement is made that occupational data (presumably job title) is a poor surrogate for the true underlying exposure distribution. A more precise statement would be that variability in actual lifetime exposure to diesel exhaust in an occupational cohort may not be reflected in differences in job title, and there might be considerable variability in actual exposure despite similar job titles.

Page 7-63, line 8: A statement is made that death certificate information is inaccurate regarding the diagnosis of lung cancer, whereas on the next page it is stated (appropriately) that lung cancer diagnosis on the death certificate is generally accurate. This is contradictory.

Page 7-67: Biologic gradient: The dose-response relationship between diesel exhaust and lung cancer is uncertain since the biologic gradient has not been defined well in the literature.

Page 7-110, first paragraph: A well as the factors noted in this paragraph, an overall limitation of the diesel-lung cancer literature is that there has not been a study conducted with workers with documented long-term exposure to diesel exhaust and long-term follow-up.

Page 7-113: The designation likely carcinogen is consistent with previous assessments, as is the group B1 designation (Page 7-112). Further justification of how the "upper end" of the spectrum designation differs from a "lower end" of the spectrum designation would add clarity for me in understanding why the terminology for upper end is used.

Page 7-113, line 4: The comment "likely to be carcinogenic at any exposure condition" is based on EPA's science policy, noted in the sections below this statement. However, taken out of this context, it implies that we know for certain that there is a measurable lung cancer risk at all environmental conditions. A better characterization might be "likely to be carcinogenic to humans by inhalation, but with greater uncertainty about the magnitude of cancer risk at environmental and low-level occupational conditions". To summarize, statements regarding risk at environmental levels should be emphasize the uncertainty about what is known about actual risk.

Page 7-114, line 9: The statement regarding environmental exposure resulting in a cancer hazard is repeated, but the qualifier "may" has been added, in contrast to the statement made on the previous page. A reason for uncertainty can include the lack of a study conducted with workers with documented long-term exposure to diesel exhaust and long-term follow-up.

It was recommended at the meeting that the rat data regarding carcinogenicity be removed from hazard identification because the mechanism of lung cancer in the rat (particle over load) is not observed in humans. I pointed out to the committee that the rat data had been part of hazard identification (but not risk assessment) since the document was first written approximately 10 years ago. I agree with the consensus to mention this on page 7-113, but not to make it part of the formal hazard assessment criteria.

Chapter 8: Dose-Response Assessment: Carcinogenic Effects

Page 8-2, lines 25-26: consider adding "at some levels of environmental exposure, although the specific levels cannot be specified" and "may pose a cancer hazard". The word hazard has an administrative meaning, if unclear, it can be interpreted to mean risk.

Page 8-5, line 13: Should read “between 10 to 20 years of work” in 1959.

Page 8-10, lines 14-18: The methods used to obtain the cumulative exposure values are controversial (exposure weighted using emission factors and assumptions about vehicle miles traveled in the absence of a more comprehensive exposure assessment), and the listing of these cumulative exposure levels is misleading if additional research proves them to be incorrect.

Page 8-11: Section on cancer risk: I prefer a narrative discussion of risk, and then showing that environmental levels have the potential to overlap at the lower range of occupational exposure, and saying that this merits control. I do not think that these risk levels should be estimated given the uncertainty about dose needed to result in cancer. In the absence of study of persons with years of exposure and follow-up, with some idea of exposure, I can’t justify these calculations. While these are interesting, I think it remains speculative to do this.

I believe that the risk calculations presented here grossly over simplifies the overall approach needed to understand the relationship between dose of diesel and lung cancer. We do not know the nature of the complex exposures experienced by workers in diesel exhaust exposed jobs. These workers were not only exposed to diesel particles, but to other particles as well. We need to understand the nature of what is captured in the job codes used in the epidemiologic studies that has come to mean cancer risk. If the risk numbers were used, it would be complete to note that the range of risk may approach zero as well.

Chapter 9: Hazard and Dose-Response

This chapter needs to be rewritten to reflect changes made in the rest of the document.

Page 9-13, lines 17-18: Carcinogenic activity is related to the small sizes of the particles. Is this known for sure in humans?

Page 9-14: Add that a limitation of the diesel literature is the need to follow-up of a cohort with well-characterized exposure over many years.

Page 9-20 to 9-21: I believe that these risk calculations as too uncertain, and favor substitution of prose describing the overlap in occupational and environmental exposures, and the uncertainty regarding the lifetime dose of diesel necessary for the development of cancer.

Page 9-22, line 24: Would say “It is presumed that low-level exposure may cause chronic inflammation…..:” Previously statements like this were phrased with greater uncertainty.

Roger O. McClellan, DVM

A. General Comments

The document with several significant revisions will be acceptable for use in regulatory decision-making. In general, the document is improved over earlier versions. However, with a preparation time that now extends over more than a decade, preparation having started in the late 1980s, it is inevitable that some portions of this document have become out-dated as other portions have been updated and improved. The key elements of the document concern the two major types of health effects attributed to diesel exhaust exposure; a) cancer and b) non-cancer health effects principally related to effects on the respiratory and cardiac systems.

The document adequately reviews potential non-cancer hazards. This version of the document is improved in that it provides a better linkage than in past revisions, to the substantial body of information available on the health hazards of Particulate Matter (PM) exposure. This information has been reviewed, and is currently being updated, as part of the process for setting the National Ambient Air Quality Standard (NAAQS) for PM. The derivation of a RFC of 14 $\mu g/m^3$ essentially equivalent to the annual $PM_{2.5}$ NAAQS of 15 $\mu g/m^3$ is appropriate. Indeed, I find no compelling evidence to not use the NAAQS $PM_{2.5}$ value for the RFC for diesel exhaust particulate matter. In my opinion, this value is conservative, i.e. more likely is overly stringent because for chronic exposure it is dependent upon key epidemiological studies for which exposure extended over earlier decades when air quality measures, and especially particulate matter concentrations, were substantially higher than the time periods immediately prior to the assessment of the health impacts. In my opinion, the use of the historical ambient air concentrations suggests the reported exposure-response functions may have been biased to the high side by a factor of 2 or more.

The 15 $\mu g/m^3$ value for an RFC for diesel based on human data is clearly preferable to using the value of 14 $\mu g/m^3$ or the suggested revised value of 5 $\mu g/m^3$ (arrived at by extrapolation from laboratory animal data). That extrapolation process is uncertain and the results are strongly dependent on the exposure levels selected for use in the original animal toxicity studies. If more exposure levels had been studied above the lowest levels studied by Manderly et al and Ishinishi et al it is quite likely that a higher NOAEL would have been found.

At the meeting, EPA staff suggested they would revise the RFC to 5 $\mu g/m^3$. Although the extrapolation process is uncertain, the use of two uncertainty factors (10 for intraspecies - human - variability and 3 for rat to human toxicodynamic extrapolation) very adequately accounts for uncertainty. Thus, the use of a factor of 30 to cover uncertainty results in an RFC with an associated high degree of confidence.

The second endpoint of concern, cancer, is more uniquely related to diesel exhaust particulate matter than PM in general. This relates principally to concern for the complex mixture of organic compounds associated with the readily respirable diesel exhaust particles. Without question, when the

organic fraction is removed from diesel exhaust particles with vigorous extraction methods and used in high concentrations in biological systems multiple effects are observed. These include cell damage, DNA damage, and mutations. What is frequently overlooked are the small quantities of the organics that are actually deposited in the human respiratory tract even with chronic exposure to diesel exhaust. As noted on page 3-29 of the document, it is calculated that continuous exposure to 1 $\mu g/m^3$ of diesel exhaust particulate matter results in annual deposition of 3 μg (the report actually uses a precisely calculated value of 2.94 μg) of polycyclic aromatic hydrocarbons (PAH) in the total lung volume. This is an important reference statement that should be repeated in several places in the report.

Consideration of this small quantity of PAH deposited helps one appreciate why with occupational exposures orders of magnitude higher than 1 $\mu g/m^3$ even in the best epidemiological studies the result is a weak signal for excess lung cancer (a relative risk on the order of 1.4). The ability to detect a weak signal of excess lung cancer risk is complicated by multiple factors. The most significant of these is the fact that many individuals in the epidemiological studies were cigarette smokers and smoking has associated relative risk on the order of 10.0. Thus, the epidemiologist is challenged to try to tease out an effect for diesel that is only about 1/20th of the much more significant risk factor—smoking. Nonetheless, the presence of a weak cancer-causing signal for diesel exhaust does raise public health concerns because of the large population exposed at low concentrations.

A critical issue is the potential for translating the weak signal into an estimate of potency; i.e., a unit risk estimates. The calculation of potency requires knowledge of both health outcome and exposure of the populations studied in the epidemiological studies. This includes exposures that occurred over decades prior to the observation of lung cancer. Unfortunately, the actual level of exposures are not known and it is impossible to reconstruct them with a high degree of certainty. I do not have confidence in the reconstructed values and, thus, urge that the reconstructed exposure values not be used to either develop unit risk estimates. In my opinion, the reconstructed exposure values are sufficiently uncertain that I do not favor their use even in "back of the envelope" approaches to create surrogate unit risk factors as done in the document on page 8-13.

In my opinion, the evidence is sufficient to characterize diesel exhaust occupational exposure at high levels as a likely human carcinogen. The risks at ambient levels of exposure are unknown and cannot be quantified. I do not think it is necessary to stretch the bounds of science to create quantitation that conveys a level of certainty that is not consistent with the available science.

On page xxi, there is a brief accounting of past versions and reviews of the document. Missing from the account is the first draft and a consultative CASAC review that took place in 1990 or early 1991. This CASAC review should be cited to make the record complete.

Chapter 1. Executive Summary

In general, the executive summary is adequate. However, it could be improved with some modest changes.

1. Page 1-2: It may be useful to cite quantitative data from EPA's Trends report in diesel emissions of particulate matter. Indeed, it may be appropriate to use a table that shows diesel emissions compared to other sources as in Table 3 of Lipfert (1998) which is based on EPA data.

2. Page 1-4, line 23-24. The references to "intensive evidence for the induction of lung cancer in the rat from chronic inhalation exposure to high concentrations of DE" must be qualified with reference made to the overload phenomena and the lack of relevance for estimation of human hazard.

3. It is critical that the Executive Summary very accurately reflect the contents of the report, including the changes proposed during the course of the October 12-13 meeting.

Chapter 2. Diesel Emissions

1. Page 2-11, line 5. Beyond referencing EPA's Trends report, I suggest a table be included that shows diesel particulate emissions compared to other sources as I suggested for the Executive Summary (see Lipfert, 1998). I feel there is great value in showing data for all major sources of particulate emissions and oxides of nitrogen. This type of comparison helps place the diesel issue in perspective.

2. Page 2-15, lines 15-19. If available, information should be provided on the sulfur content of railroad-grade diesel fuel compared to on-road fuel.

3. Page 2-15, lines 20-23. The discussion should be expanded to include consideration of lubricating oil contributions to the solvent extractable organics and not just PAHs.

4. Page 2-43, Figure 2-37. Information should be provided on where relative to the origin of the particles in the combustion cylinder and exhaust system the number/mass particle size measurements were made. Kittleson may have more recent data on how number/mass size distribution changes with distance and time relative to point of formation. (See also pg 2-45, lines 25-28.)

5. Page 2-61. Exposure: to provide some historical perspective, this section might include one or more figures from Lipfert (1998). (See Figures 5 and 6.) Consideration of these historical levels of PM is needed to appropriately interpret the findings of epidemiological studies of both PM and diesel exhaust particulate matter.

Chapter 3. Dosimetry of Diesel Particulate Matter

This chapter in its present form is marginally adequate for use in evaluating the health hazards of exposure to diesel exhaust. The chapter could be substantially improved with modest additions and changes. Specific suggestions are given below:

1. The present chapter does not represent a balanced coverage of dosimetry information on humans and laboratory animals. Obviously, our primary interest is in humans and, thus, human data should be emphasized when it is available with laboratory animal data used only when required to fill gaps in our knowledge of humans. Page 3-2, lines 3-7 needs to be revised to recognize that it is only necessary to become concerned with "human equivalent concentrations" derived from laboratory animals when sufficient human data are not available.

2. The chapter should give broader coverage of the total respiratory tract because inhaled diesel exhaust particles deposit on the total tract from the nares to the alveal: not exclusively the lung as stated on page 3-1, lines 30-31.

3. Section 3.3.1 on Deposition Mechanisms is adequate but could be enhanced with use of the well-known (to experts in the field, but not all readers) figures on deposition mechanisms. The section appears to understate the deposition of diesel exhaust particles in the nares by diffusion.

4. Section 3.3.1.1 would be enhanced by inclusion of a figure showing regional deposition of particles in humans as influenced by particle size. This general view should be presented before the present Figure 3-1. It might also be useful to show similar curves for the most commonly studied laboratory animal species such as the rat. These are available from earlier reviews by Schlesinger and others.

5. Section 3.3.2 on Particle Clearance and Translocation could be enhanced by including a figure showing typical clearance patterns (as a function of time after single exposures) for humans and perhaps the rat. The date of Bailey et al (1982) might be used. It is cited on pg. 3-9, lines 33-35.

6. A version of Figure 3-5 (referenced on page 3-19) should be used that includes the predicted lung burdens for the 3.5 and 7.1 $\mu g/m^3$ levels for comparison with the observed lung burdens. This helps illustrate the impact of the impaired clearance and overload. I can provide a figure if the staff cannot locate one.

7. Section 3.3 should include a discussion of the NCRP and ICRP respiratory tract models. This should include one or more illustrations of model results for chronic exposure. The modeling results should then be compared with the predictions made by Xu and Yu, 1987 and presented in Table 3.1. This kind of comparison was requested in the last CASAC review.

8. The information presented in Section 3.5.4 on Bioavailability/Deposition of Organics needs to be verified and the results compared with those developed using the NCRP and ICRP models. All relevant parameters including assumptions should be explicitly stated. The results presented in this section are very important to later discussion involving effects measured in vivo as well as in in vitro assays. The fact that exposure to 1 $\mu g/m^3$ of diesel exhaust continuously only results in deposition of about 3 μg of PAHs per year in the total human lung helps reconcile the results of in vitro assays with very large doses and the weak cancer signal in heavily exposed occupational populations.

9. The summary section (3.6) on modeling is inadequate. The information requested above (items 8 and 9) could be presented here. However, a quantitative treatment and comparison of the models is required.

10. The footnote to Table 3-1 has typos related to expressions of surface area in cm^3 rather than cm^2. Reference is made to human data on total lung volume, total airway surface area and the surface area of the unciliated airways. Similar data should be presented for rats and hamsters. In addition, other critical respiratory parameters should be presented for all three species (humans, rats and hamsters).

11. The source for Figure 3.3 is unclear.

Chapter 4. Mutagenicity

This chapter in its present form is adequate for use in evaluating the health hazards of exposure to diesel exhaust. The chapter would be substantially improved by including (a) a contextual setting as to why mutagenicity of diesel exhaust is of interest, (b) a historical context, and (c) a context for considering the relatively large doses of diesel exhaust particulate extracts used in the various in vitro and in vivo assays. Recall the EPA calculation that continuous exposure to 1 $\mu g/m^3$ of DPM results in annual deposition of 3 μg of PAHs in the total human lung. This result from Chapter 3 should be summarized in Chapter 4.

1. Page 4-1. A brief paragraph should be added concerning the linkage between mutagenicity and carcinogenicity. Hence, the basis for the high degree of interest in the mutagenicity of diesel exhaust. This is done later but it would be helpful as part of a "road map" up front.

2. Page 4-1. A brief paragraph should be added providing a historical context for the research on mutagenicity of diesel exhaust particle extracts. This would include a reference to the paper of Kotin et al (1955) that describes the presence of aromatic hydrocarbons in diesel exhaust and the carcinogenicity of the extracts when painted on mouse skin. (Kotin, P.; Falk, H. L.; and Thomas, M., 1995. Aromatic Hydrocarbons: 111. Presence in the Particulate Phase of diesel engine exhausts and the carcinogenicity of exhaust extracts. Ind. Health 11: 113-120.) The results reported in this paper coupled with the availability of the Ames test in the 1970s triggered EPA's early efforts to evaluate the

mutagenicity of diesel exhaust. Note should be made of two aspects of EPA's early program: (a) its orientation to attempting to use a comparative potency approach (short-term mutagenicity and cell transformation assays, skin painting/carcinogenicity assays, short-term animal studies, and epidemiological evidence on roofing tar, coke oven emissions, and cigarette smoking) to estimate diesel exhaust risks and (b) biological activity-directed chemical fractination/characterization. This would include references to several papers by Roy Albert who championed the comparative potency approach and Joellen Lewtas who guided the biological activity directed chemical fraction work. This work is covered starting at the bottom of page 4-1, but should be introduced in opening paragraph of the chapter. A reference on the comparative potency approach that might be included is Cuddihy, R. G.; W. C. Griffith, and R. O. McClellan, 1984, Health Risks from Light Duty Diesel Vehicles," Environmental Science Technical 18: 14A - 21A. A related reference is McClellan, R. O., R. G. Cuddihy, W. C. Griffith, and J. L. Manderly (1989); Integrating Diesel Data Sets to Assess the Risks of Air Pollutants in Assessment of Inhalation Hazards. (U. Mohr, D. R. Bates, D. L. Dungworth, P. N. Lee, R. O. McClellan, and FJC Roe, page 3-22 ILSI Monograph International Life Science Institute, Springer-Verlag, Berlin, Germany. Although the comparative potency approach has been replaced, the use of direct, but highly uncertain epidemiological evidence, the approach still deserves brief coverage.

3. A brief paragraph should be included to place the dosages used in the mutagenicity assays in to perspective relative to plausible human exposures. This would include use of Figure 3 from McClellan (1986) (McClellan, R. O., "Opening Remarks: Toxicological Effects of Emissions from Diesel Engines (1986). In: Carcinogenicity and Mutagenicity of Diesel Engine Exhaust. N. Ishinishi, A. Koizum, R. O. McClellan and W. Stober, Eds. Pg. 3-8, Elsevier Science Publishers, Amsterdam.) Reference should also be made here to the material presented on page 3-29 of Chapter 3 on Dosimetry. That section notes that an individual inhaling 1 μg diesel exhaust particulate matter/m^3 for 1 year would deposit 420 μg of DEP and 2.94 μg of PAHs in their lung.

4. Page 4-1: Close to the reference of proceedings of symposiums on the health effects of diesel emissions, reference should also be made to the Health Effects Institute document that reviewed the health effects of diesel exhaust. Several chapters in that excellent review cover the issue of genotoxicity and its linkages to carcinogenocity.

5. Page 4-4: A recent paper from Japan on gene mutations evaluated in rodents with a marker gene and exposure to diesel exhaust should be cited. I do not have this reference at hand. Although it notes an increase in gene mutations in the lung it fails to cite the classical studies by Driscoll and Oberdorster which show that the mechanisms of mutagenic response to soot particles is likely via an inflammation/oxidative stress pathway.

Chapter 6. Quantitative Approaches to Estimating Human Non-Cancer Health Risks of Diesel Exhaust

This chapter is acceptable for use in evaluating the human health hazards of exposure to diesel exhaust. It could benefit from rigorous editing to improve the clarity and make it more concise. The following points require specific attention.

1. Page 6-4, line 32: Reference should be made to the recent re-analysis of the Harvard Six-Cities Study and the American Cancer Society Study performed under Health Effects Institute sponsorship by a team led by Professor Dan Krewski. The results of the re-analysis should be briefly summarized. In addition, the recent multi-city study performed by Professor Jon Samet and associates under Health Effects Institute sponsorship should be cited and the results briefly summarized.

In discussing the results of the Harvard Six Cities and the American Cancer Society Study, reference should be made to Lipfert (1998), who has emphasized the importance of considering historical changes in air concentrations of particulate when estimating exposure-response relationships. Lipfert (1995) indicates that when historical TSP values were substituted for more current values in a re-analysis of the Harvard Six Cities Study the regression coefficient for the exposure-response relationship was reduced by a factor of 2.6. (Lipfert, F. W. (1995) "Estimating Air Pollution - Mortality Risks from Cross-Sectional Studies: Prospective vs. Ecological Study Designs." In: Particulate Matter: Health and Regulatory Issues, pp 78-102. AWMA Pub. No. VIP 49. Proceedings of the International Specialty Conference, Pittsburgh, PA.) More recently, Lipfert (1998) has reviewed data on historical changes in particle concentrations and discussed how these changes should be considered in the analysis and interpretation of American Cancer Society Study reported by Pope et al. Lipfert (1998) indicates that the failure to use this exposure data from the earlier time period biased Pope et al's regression coefficients for exposure-response relationships upwards by a factor of 2 to 5.5. He indicates regression coefficients based on air quality data for the earlier time period could have yielded coefficients in the range of 0.0013 to 0.0035 per $\mu g/m^3$. (Lipfert, F. W. (1998), "Trends in Airborne Particulate Matter in the United States." Appl. Assup. Environ. Hyg. 3 (6): 370-384). The time trends in ambient air concentrations of particulate and other pollutants need to be considered in evaluating health effects studies associating effects in morbidity and mortality with long-term exposure to pollution. It may also be informative to consider the changing patterns of emission sources.

2. Page 6-6, lines 27-34: The approach outlined in this section has very little support and should be eliminated. If the paragraph is left in it should be placed after more plausible approaches. On line 27 the word "view" should be replaced by "assume" and on line 28 the word "treat" should be replaced by "assume." If the approach taken here were to be used it would also have to assume that particles other than DPM are without any health effects.

3. Page 6-7, lines 9-12: The approach proposing apportionment of the 15 $\mu g/m^3$ NAAQS for $PM_{2.5}$ to different sources, in this case to diesel, is inappropriate. This is not an appropriate part of the setting of an inhalation reference concentration and this sentence should be removed. Instead, I might suggest "The approach of assuming equal potency for $PM_{2.5}$ and diesel exhaust suggests that an

appropriate inhalation reference concentration for DPM is 15 $\mu g/m^3$, a value equal to the annual NAAQS for $PM_{2.5}$."

4. Page 6-9, lines 4-6: The reader is provided a one sentence pointer to a 10 page appendix (B) on "Benchmark Concentration Analysis of Diesel Data." If this Appendix (B) is worthy of inclusion, then it should be presented more clearly in the text. I suggest the appendix remain and that a paragraph be used to introduce the approach on page 6-9 and then a paragraph used on page 6-13 or 6-14 to indicate clearly why the Benchmark approach is not being used.

5. Page 6-10, lines 22-24: This sentence should be removed from the text and added as a footnote to Table 6-1.

6. Table 6-1: The footnote notes for the table need to be reviewed and revised. A key footnote was place in the text (see above) and others are apparently note used.

7. Page 6-11, HEC Derivation: This section suffers from inadequacies noted in the Dosimetry chapter and is excessively long and complicated. Part of the difficulty relates to excessive reliance on the model of Yu (1991) and the failure to make quantitative use of NCRP and ICRP models for particle deposition and clearance. The section could be improved if reference were made to a key table as I have suggested for inclusion in the Dosimetry chapter that would detail all of the relevant input parameters (including assumptions) for rats and humans used to calculate a "Human Equivalent Concentration" for diesel exhaust particles. The table would show input data and output for the Yu, NCRP and ICRP models and be accompanied by text explaining similarities and differences in results. The present Dosimetry chapter does not contain such a table.

The existing section 6.5.2 HEC Derivation could be substantially shortened if a table such as described above were included in the report.

8. Table 6-2: This table could be improved by including a column that normalizes all the rat exposure data to mg/m^3 or $\mu g/m^3$ based on continuous exposure. This is the first step in evaluating the HEC. Burying this normalization in the HEC values given mystifies the HEC evaluation process. Indeed, I am concerned that excessive reliance on the Yu model has unnecessarily complicated the HEC calculation process and may have introduced distortions in the basic data. For example, the ratio of the exposure concentration (not normalized to continuous exposure) to the HEC for the lowest exposure level (0.35 mg/m^3) for the Manderly et al (1987a) study is about 10 to 1 while for the 3.5 and 7.0 mg/m^3 levels it is nearly 2 to 1. For the Ishinishi et al (1988) study the change in this data from the lowest exposure concentration to the highest shifts from 3 to 1 to about 0.8 to 1. The difference between the Manderly et al and Ishinishi et al studies at a given exposure concentration is primarily due to the difference in exposure time (35 hours per week versus 96 hours per week). Presumably, the remainder of the differences including the shift from low to high exposure concentrations results from Yu's modeling of overload. I submit that Yu and the EPA staff have gotten carried away with

modeling, perhaps best characterized as "mathematical gymnastics," and would do better by focusing on the basic data. I suspect it may not change the basic RFC calculation since reliance is based on the low exposure concentration data. The key question is whether one feel comfortable saying that rats exposed to 0.46 mg/m^3, 16 hours/day, 6 days/wk (normalized 0.38 mg/m^3) and humans exposed to 0.144 mg/m^3 are equivalent exposures in terms of dose to lung. This difference appears about right and is largely related to differences in fractional deposition for rats and humans. This element of simplicity is lost in the mathematical details of Appendix A.

9. Pages 6-13, line 16: A brief paragraph should be added here explaining why the Human Equivalent Concentration to rat exposure concentration relationship is not proportional over the range of exposures described. This should include a brief statement as to why the shift occurs, is it all attributable to overload? If so, what is the evidence for "overload" occurring in humans? This situation might be clarified when a comparison is made to results from use of the ICRP and NCRI models.

10. Page 6-13, lines 18-19: Change to read "with no observed adverse effect levels as high as 0.144 mg/m^3.

11. Page 6-13, lines 20-21: Change to read "in the continuum from 0.33 to 1.95 μg/m^3."

12. Page 6-13: Much of the discussion on this page and page 6-14 fails to recognize that the relationships observed are in part a function of study design. For example lines 35-36 note that the highest no-effect HECs of 0.128 mg/m^3 and 0.144 mg/m^3 are nearly five-fold above other no-effect levels of 0.032 and 0.038 mg/m^3. So what! If Manderly et al had elected to study a concentration higher than 0.35 mg/m^3, 7 hr/day, 5 day/wk, than one could have calculated a NOAEL HEC closer to 0.144 mg/m^3. Likewise, it is quite possible that if studies had been conducted at levels above that identified as the highest NOAEL but below the LOAEL, an ever-higher NOAEL might have been identified. This should be clearly stated in the text.

13. Page 6-13, line 36 and page 6-14, line 3: The basis for electing to not use the $BMCL_{10}$ needs to be expanded. One could argue that a calculated $BMCL_{10}$ of 0.37 μg/m^3 combined with a HEC-NOAEL of 0.144 mg/m^3 provides a basis for selecting a value of 0.25 to 0.30 mg/m^3 as a starting point for calculations of an RFC.

14. Page 6-15, line 19: Expand to read "0.46 mg/m^3, 16 hours/day/6days/week"

15. Page 6-17, line 13: Remove the phrase "the apportionment estimates of 1.5 - 5 μg/m^3". As discussed earlier, the issue of apportionment is not a part of the science underlying selection of an RFC.

16. Page 6-17, line 28: Revise to read "this DE RFC value of 14 μg/m^3 or a revised DPM-RFC of 5 μg/m^3 is reasonably congruent with the annual $PM_{2.5}$ NAAQs of 15 μg/m^3 established to protect against adverse effects of ambient air fine particles typical of the current U.S. environment. If a revised

DPM-RFC is calculated using an uncertainty factor of 10 for intraspecies variability and 3 for interspecies (toxicodynamic considerations), then I think the resulting RFC should be viewed as having a high degree of confidence.

17. Page 6-21: Expand to read "0.46 mg/m^3, 16 hours/day, 6 days/week, a NOAEL."

18. Appendix A: This is an extraordinarily detailed presentation that would benefit greatly from inclusion of an easy-to-read summary. Such a summary would include a table such as I have advocated elsewhere, summarizing all of the critical input and output parameters for modeling the disposition of particles in rats and humans exposed to diesel exhaust particles. It may be necessary to modify Appendix A to include details related to use of the ICRP and NCRP models.

Chapter 7. Carcinogenicity of Diesel Exhaust

1. Page 7-2, line 32: As noted elsewhere, in considering the Harvard Six Cities and American Cancer Society Studies, it is important to make note of the historical changes in air quality (Lipfert, 1998).

2. Page 7-5, lines 8-10: The figures presented here on sales of diesel-powered trucks need to be qualified by making reference to the portion of the on-road truck fleet that was dieselized. Perhaps this portion of Chapter 7 can be better linked to Chapter 2 on diesel emissions.

3. Page 7-113, Weight-of-Evidence: This section needs to be rewritten. In my opinion, it is not appropriate to use the rat lung tumor data inhalation study as part of the weight of evidence for human carcinogenicity. It is totally inappropriate to include data from rats given intratracheal inhalations as part of the weight of evidence in the face of the compelling mechanistic data from well-conducted inhalation studies showing a lack of relevance of the rat data for assessing human hazard for diesel exhaust particulate matter exposures. Indeed, the most relevant rat data are from the many rats studied at levels not producing an overload and these were negative for cancer induction (Valberg).

4. Page 7-113, line 27-31: In my opinion the following statement is not adequately supported and should be eliminated "Nonetheless, available data indicates that DE-induced lung carcinogenicity seems to be mediated by mutagenic and non-mutagenic events by both the particles and associated organic compounds, although a role for the organics in the gaseous phase cannot be ruled out. Given that there is some evidence for a mutagenic mode of action, a cancer hazard is presumed at any exposure level." In my opinion, the argument for a role for mutagenic events has not been clearly articulated and, thus, the case for a linear extrapolation to levels of a few ：g/m^3 has not been made. Consequently, this assumption is clearly a default and should be stated as such. The summary statement provided on page 114, lines 29-30 is appropriate. (Perhaps it was written by a different author.)

Chapter 8. Dose-Response Assessment: Carcinogenic Effects

1. Page 8-2, lines 29-31: While it has been shown unequivocally in several studies that DE can cause benign, and malignant lung tumors in rats in a dose-related manner following chronic inhalation exposure to sufficiently high concentrations, it has also been shown that low, but still substantial exposures to diesel exhaust do not cause an excess of lung cancer in rats (Valberg). Further, it has been clearly demonstrated that the rat lung tumors occur via a mode of action (particle overload, inflammation, reactive oxygen species, mutations and lung cancer) that is unlikely to be operative in humans at ambient levels of exposure. Thus, the quoted sentence should be removed. The sentence is not consistent with lines 13-21 on page 8-3. The EPA staff should accept the evidence for human cancer risk from diesel exhaust for what it is—weak—and avoid overstating the evidence.

2. Page 8-3, line 27: I suggest adding: "In addition, it is difficult to ascertain the role of ambient particulate matter that was at substantially higher concentrations for much of the life of the occupationally exposed individuals than was the case when the epidemiological studies were conducted (Lipfert, 1998).

3. Page 8-4, line 10: I suggest you insert "For example, relative risks on the order of 10 are frequently observed for lung cancer in smokers compared to relative risks for diesel exposed workers for up to about 1.5"

4. Page 8-5, line 4: I suggest it be revised to read studies have "reconstructed quantitative historical exposure data" to emphasize the exposure data was reconstructed. I suggest that any time reconstructed historical exposure data is cited it should be specifically cited as reconstructed historical exposure data.

5. Page 8-6, lines 4-20: It would be appropriate to give the confidence intervals for the odds ratio of 1.64 and 1.41. In addition, the odds ratios and the associated confidence intervals for smoking as reported by the author should be given. This helps provide the reader with perspective as to the weak evidence for cancer risks from diesel exhaust exposure vs. cigarette smoking.

6. Page 8-9, line 8: add "lack of knowledge of whether the men actually drove diesel trucks."

7. Page 8-9, lines 9-17: I think the authors should state more strongly the high degree of uncertainty associated with retrospectively reconstructing exposures for 1948 to 1983 from 1990 exposure assessments.

8. Page 8-10, line 9: I think the value is "about 15-fold" rather than five-fold.

9. Page 8-10, lines 12-24: I suggest that any time an exposure value is presented, especially when presented to three significant figures, it should be prefaced by "estimated." And, as noted elsewhere, it should be stated that ambient particulate exposures, including EC, were undoubtedly much higher for a major portion of the life of the individual.

10. Page 8-11, lines 4-7: With reference to activities underway, it would be appropriate to note both the Australian miner study and the NIOSH miner study.

11. Page 8-12, lines 27-29: It is inappropriate to state a 5% background lifetime lung cancer risk for the U.S. population without giving data showing how non-uniformly this risk is distributed across the total population. For example, the lifetime lung cancer risk for non-smokers is about 1% compared to 10% for smokers with about 85% of the cases in this total population attributable to cigarette smoking. Since a relative risk approach is being used it follows that 85% of the estimated cases attributed to diesel exposure will occur in smokers. Thus, for non-smoking workers the excess risk attributable to diesel exhaust exposure would be about 0.4% and for smokers about 4%. In similar fashion the subsequent risk numbers need to be lowered by a factor of 5 for non-smokers and elevated by a factor of 2 for smokers. And one could go on and on playing a game of "mathematical gymnastics. The more one plays the game of "mathematical gymnastics," the more obscure the underlying data becomes and the greater the likelihood of losing contact with reality. I suggest that we call time-out on "mathematical gymnastics" and agree the existing epidemiological data are inadequate for quantitation. The facts are that we have a weak signal for potency and a potentially large population exposed to low levels of diesel exhaust on the order of a : g/m^3.

12. Page 8-13, lines 28-29: If the Agency is concerned about non-road sources of diesel exhaust, then why didn't they include more information on non-road sources. The statement seems to imply that only a portion of the U.S. population is exposed to diesel exhaust from non-road sources. Intuitively, I suspect the non-road sources contribute generally to exposure across the U.S. But the real question is where is the data? The statement "children who may be more sensitive to early life exposure" appears to be almost a throw-away. Again, what is the evidence?

13. Page 8-13, line 30 and earlier: I am concerned about the excessive quantitation based on very limited data. I doubt that this paragraph sufficiently qualifies the "mathematical gymnastics" exercises. If these numbers are left in, I suggest words be added as follows - "There is a low degree of confidence in the risk numbers cited and, therefore, they should not be construed in any way be equivalent to the unit risk values the agency has sometimes calculated."

14. Page 8-14, lines 6-7: I suggest it would be appropriate to reword as follows - "Nevertheless, these analyses indicate that environmental exposures on the order of a $\mu g/m^3$ may pose a lung cancer hazard even though a level of zero risk cannot be excluded."

15. Page 8-15, line 4: Remove the reference to environmental cancer risks from DE ranging from 10^{-5} to 10^{-3}.

16. At several places in this chapter it is very important to emphasize that the basic epidemiological data shows an association between employment in the trucking and railroad industry and a weak cancer signal. It is important to emphasize that the epidemiological studies were not based on exposure to

DPM but rather job classification, duration of employment, etc., and an evaluation of association with lung cancer. In a second step, estimates of exposure to DPM are introduced as a means of extrapolation to ambient air concentrations and the general population. There is a high degree of uncertainty in extrapolating from these very complex occupational situations to the general population and from high levels of exposure to DPM and many other agents to substantially lower ambient levels of DPM.

APPENDIX C

As noted earlier in my comments, the estimation of exposure becomes a critical part of calculating the potency (i.e., slope of the dose-response function) for past exposures increasing mortality. This point should be made in Appendix C when the Harvard Six Cities and American Cancer Society Studies are cited. It will be appropriate to reference the Lipfert (1995 and 1998) papers and note the impact of using estimates of exposure from historical air quality data. It may be appropriate to include one or more of the figures from the Lipfert (1998) paper.

Günter Oberdörster, PhD

Chapter 3: Dosimetry of Diesel Particulate Matter

This revised chapter is significantly improved, and the comments made at the previous review have generally been addressed. References to the PM document have been made throughout the Chapter, and some figures have been included. It would still be useful to include also a figure showing the deposition efficiency in humans over the whole particle range from ultrafines to 100 ∶m, for example, as it has been derived by ICRP. The comments made below relate to a few additional issues which should be answered and incorporated in this draft.

Page 3-1, line 2: I suggest to delete "clearly" and start the sentence with "Animals and humans …."

Page 3-3, line 6: I suggest to delete "many".

Page 3-6, lines 25/26: The insignificant rate of clearance by dissolution pertains only to the core of DPM, not the whole DPM. Furthermore, there is also a significant difference between rats and humans with respect to the importance of clearance by dissolution. Due to the long alveolar macrophage-mediated clearance in humans — in contrast to rats — dissolution of even "poorly soluble particles" can be a significant contributor for humans as has been pointed out by Kreyling.

Page 3-7, line 3: Clearance of PSP deposited in the oral passages is not by coughing.

Page 3-8, lines 5/6: One study is indicated here to show a difference in tracheal transport with respect to age. The reference is missing, and can that one study be used to generalize age-related differences?

Page 3-9, lines 4-10: It is speculated here as to why PAH on the diesel particles may have an effect in humans but not in rats. One possibility suggested here is the greater interstitial localization of inhaled diesel particles in the primate lung compared to rat lungs, based on the paper by Nikula *et al*. One has to be cautious with this interpretation of the paper since translocation rates from the alveolar to the interstitium may be quite different between rats and primates, similar to the alveolar macrophage-mediated clearance rates being much faster in rats than in humans. Thus, an evaluation of interstitial *vs*. alveolar particles made at one point in time only (at the end of a two-year study in rats and monkeys) probably does not give an accurate picture of the kinetics of such translocation and the importance of the interstitial compartment of one *vs*. the other species.

Page 3-16, lines 11/12: It should be emphasized here that the studies by Adamson and Bowden used high doses by intratracheal instillation and that this will lead to significant direct particle–type I cell interactions in the lung. The mechanism of interstitial access of particles at very high doses given as a bolus is likely quite different from that at much lower inhaled doses.

Page 3-16, lines 24-29: As mentioned before, the study by Nikula *et al*. needs to consider that only one point in time after exposure to different particles in rats and monkeys was used to determine the relative ratios of dust accumulation in the alveolar space *vs*. the pulmonary interstitium. As is well known from other studies, there is significant accumulation of dusts inhaled at higher concentration by rats in their tracheobronchial lymph nodes, *i.e*., these particles have to be transported there *via* interstitial access; if the clearance rate from the interstitium into lymphatic tissues is faster in rats than in monkeys this could account for the observation that relatively less interstitial particles were found in the rat as compared to monkeys. This may give rise to an incorrect conclusion with respect to species differences of the persistence of interstitial *vs*. alveolar particles.

Page 3-18, line 13: Change "pathophysical" to "pathophysiological".

Page 3-19, lines 16-18: Reference is made here to Figure 3-5. There is a typo in the figure legend and in the labelling of the ordinate, change PPM to DPM.

Page 3-19, lines 30/31: The revised version of the Pock model for rats by Stöber is described here, including an interstitial space compartment for retained particles that increases greatly. This model appears to be in contrast to the conclusions by Nikula *et al*. if one reads the document in its present form. However, as suggested above, the data by Nikula *et al*. represent only one point in time and may have to be viewed in the context of different interstitial clearance rates between rats and monkeys.

Page 3-20, line 8: The overloading effect has also been noted in mice and hamsters, not only in rats. See studies by Muhle *et al*.

Page 3-20, lines 23/24: It is not only a suggestion that macrophage-mediated clearance is slower in humans than in rats, but it is, indeed, a fact that has been reaffirmed repeatedly.

Page 3-20, line 25: It should be clarified what significant differences in macrophage loading between species are alluded to here.

Page 3-21, lines 28/29: It is noted here that no lung cancer was reported among miners with apparent particle overload. However, it should also be noted that the same is true for rats where particle lung overload can occur without the induction of lung tumors. See for example the study by Lee *et al.* where 50 mg/m^3 of TiO_2 exposure over two years resulted in significant particle overload but no increased lung tumors.

Page 3-22, lines 32-35: In addition to the suggestion that surface characteristics of alveolar macrophages are altered so they adhere to each other, it has also been suggested that alveolar macrophages activated by phagocytized particles release chemotactic factors that in turn attract other macrophages leading to cluster formation. This was suggested by Bellmann *et al*. (*J. Aerosol Science* **21**:

377-380, 1990) where a clearance and retention model with a specific alveolar macrophage compartment is described.

Page 3-23, line 32: Change "of" to "at".

Page 3-29, line 10: I suggest to change "calculate" to "estimate".

Page 3-36, lines 21-36: This paragraph describes clearance rates for poorly soluble particles in humans for larger particles and an adjustment to smaller ones. However, the adjustment being used for the smaller particles are clearance rates determined for the rat by Snipes (1979). Moreover, the clearance rates for these smaller particles are taken from an annual report of ITRI, *i.e.*, these data were not peer-reviewed. It is, thus, not understandable why the rat clearance rates should be used for humans; and it is also not clear which larger particle size alluded to in line 29 is meant, is it 0.4 ：m or 2 ：m? Likewise, it is not clear why this choice would underestimate rather than overestimate (line 30) the correct clearance rate for DPM.

Page 3-37, lines 24/25: It is pointed out here that the Yu model has a significant clearance into the lymphatic system, *i.e.*, *via* interstitial compartment. This needs to be kept in mind, because later in the document (see below) it is stated that the Yu model does not have an interstitial compartment. (See also publication by Hsieh and Yu, 1998, *Inhalation Tox*.).

Page 3-38, lines 22-33: Line 22 mentions the lack of an interstitial compartment in the Yu model, which is not quite correct since an interstitial pathway in the Yu model for lymphatic clearance is certainly provided. In this paragraph the work of Kuempel and Nikula is also mentioned as providing compelling evidence on the significance of an interstitialization process in primates. Again, as stated before, rats also have a significant amount of particles cleared into the interstitium and the regional lymph nodes, and this clearance is considered in the Yu model as well since in this model the alveolar clearance rate consists of the macrophage-mediated and the interstitial clearance. Specifically in the particle overload situation, this pathway appears to be rather rapid in rats. Thus, the difference between rats and humans may be the rate of clearance into and out of the interstitium, similar to the differences in alveolar macrophage-mediated clearance rates between rats and humans.

Line 30 states that the findings in retired coal miners are consistent with the existence of an interstitial compartment. However, these findings are also quite consistent with overload induced retardation of alveolar macrophage-mediated clearance, as has been pointed out before.

Page 3-39, lines 34/35: The lack of the interstitial compartment in the Yu model is again addressed here which may have to be revised.

Page 3-40, lines 17/18: The statement here that dissolution is insignificant for poorly soluble particles compared to clearance as an intact particle is not necessarily true for humans because of the much

longer alveolar macrophage-mediated clearance in humans *vs*. rats. This was pointed out by Kreyling repeatedly.

Page 3-40, lines 22: The prominence of interstitialization poorly soluble particles in primates *vs*. rodents should be considered in light of possibly much faster clearance rates for this pathway in rodents, as mentioned several times before.

Page 3-40, line 25: Replace "may" with "is". It is, indeed, a fact that prolonged exposure to high concentrations of particles will lead to particle overload.

Also, replace "appears" with "is" in line 30. It has been well established that, indeed, macrophage-mediated clearance is slower in humans than in rats.

Page 3-41, line 31: The MMAD of 0.2 ∶m should more appropriately be called a mass median thermodynamic diameter.

In general, this chapter should also emphasize more the variability in outcome between different models with respect to deposition and clearance as well as the biological individual variability in particle deposition and clearance which can lead to significant differences in estimates of retained particle burdens. Thus, a cautionary note that the use of the C. P.Yu model should not be viewed as an endorsement that it is the most appropriate one to use. The predictions derived from this model as well as from other models still have potentially large uncertainties.

Chapter 4: Mutagenicity.

This chapter does not include revisions that were requested repeatedly in all previous reviews of the document, *i.e*., addressing the issue of very high doses which were used in mutagenicity assays relative to doses that can reasonably be expected to occur *in vivo*. The EPA should take this suggestion a bit more seriously and include a statement in this section regarding the high dose levels being used.

Chapter 9: Characterization of Potential Human Health Effects of Diesel Exhaust: Hazard and Dose–Response Assessments

Based on the extensive discussions that the Panel had at the CASAC meeting this chapter will be revised accordingly by EPA. Most of the following comments are repetitive since they were submitted prior to these discussions and have been addressed at the meeting.

Obviously, EPA staff is struggling in this chapter to find the right wording for the degree of carcinogenicity for diesel exhaust which sometimes leads to awkward sentences. For example, statements like "the human evidence for potential carcinogenicity for DE is judged to be strong but less than sufficient" (page 9-11, lines 15/16), or "DE is likely to be carcinogenic to humans by inhalation at any exposure

condition" (page 9-13, lines 29/30). Another sentence states (page 9-12, lines 13-15) that "the animal evidence provides additional support for identifying a potential cancer hazard to humans, but is considered not suitable for subsequent dose–response analysis and estimation of human risk with DE".

This needs to be resolved: If the evidence is not sufficient, it cannot be that strong; carcinogenicity of DE at any condition is hard to accept; and if the animal evidence cannot be used for human risk extrapolation (because of an irrelevant mechanism) then they cannot provide additional support for identifying a potential cancer hazard to humans.

The derivation of an RfC — summarized in this chapter — is not quite clear, specifically the justification that the value of 14 : g/m^3 for the RfC agrees with the NAAQS of 15 : g/m^3, and at the same time it being close to the 1.5 - 5.0 : g/m^3 derived from the apportionment of the $PM_{2.5}$ standard. The RfC apparently was derived by using just one uncertainty factor of 10 for more susceptible parts of the population, whereas no factor for rat to human extrapolation was used. This is justified by the use of a dosimetric extrapolation model and by a statement in Chapter 6 that rats are more sensitive than humans. However, the use of the dosimetric deposition, retention and clearance model addresses only to some extent the uncertainty for interspecies extrapolation, since deposition and clearance models in general have some degree of uncertainty. Thus, the use of such model does not eliminate completely the need for an uncertainty factor which is normally 10 (3 for toxicokinetics, 3 for pharmacodynamics). In view of data by Rudell *et al*. (1999; see below) showing that humans exposed for 1 hr. to 0.3 mg/m^3 show significant inflammatory cell responses in lung lavage, one could argue that humans are at least as sensitive or more sensitive than rats, and that an additional factor of 3 for rat to human extrapolation is justified. That would indeed bring the present RfC of 14 : g/m^3 down to around 5 : g/m^3 for DE. This is a very low value, and I consider the confidence in this RfC to be moderate to low, given that it is based on a number of assumptions.

Attached are the abstracts of two publications by the Swedish group, with Rudell as the first author (Rudell *et al*., Efficiency of automotive cabin air filters to reduce acute health effects of diesel exhaust in human subjects. *Occup & Environ Med*. **56**(4): 222-231, 1999; Rudell *et al*., Bronchoalveolar inflammation after exposure to diesel exhaust: comparison between unfiltered and particle trap filtered exhaust. *Occup & Environ Med*. **56**(8): 527-534, 1999). The studies show that human subjects exposed to diluted diesel exhaust at 300 : g/m^3 for 1 hr. experience significant inflammatory responses with respect to lung lavage cells. If one contrasts this with results from a two-year rat inhalation study with diesel exhaust (Henderson *et al*., 1988, *FAAT* **11**: 546-567) at the lowest exposure concentration of 350 : g/m^3, it turns out that in the rat study exposure at this concentration for 3 months (intermediate sacrifice timepoint) did not show any significant inflammatory responses in the lung lavage. Thus, a greater sensitivity of rats with respect to non-cancer effects cannot be assumed, as is stated in the present draft of the document.

The studies by Rudell *et al*. (attached abstracts) should also be included in Chapter 5 of the document, Non-Cancer Health Effects of Diesel Exposure. These authors show, in addition to inflammatory responses in humans after short-term exposures, that by including a particle trap in the exhaust

the inflammatory response in humans was still the same and that only the inclusion of an activated carbon filter eliminated the response. This result demonstrates that not the particles but the gaseous exhaust components are responsible for the inflammatory cell response.

The decision not to use the rat lung tumor response data for human extrapolation is in line with the recommendation of CASAC since the rat tumors are induced by mechanisms which certainly will not be operating at low environmental exposures in rats or in humans due to the existence of a threshold in particle overload studies. There is some speculation in this chapter and in other parts of the document (Chapter 8) as to why there may be differences between induction of lung tumors in rats at high concentrations and a suggested carcinogenicity for DE for humans at low environmental concentrations. This difference is hypothesized to be due to mutagenic and genotoxic effects of organic compounds in the gas and particle phase and other effects related to induction of reactive oxygen species by the organics.

However, one other aspect that is not discussed in the document relates to potentially significant differences in the exposure atmospheres of the chronic high dose rat studies *vs*. the low environmental levels of diesel exhaust. At low environmental concentrations, as is described in Chapter 2 of the document (Figure 2-37), there are two distinct particle modes of diesel exhaust, the ultrafine particles and the accumulation mode particles. In contrast, the high concentrations in the mg/m^3 range used as primary dilution in the animal exposure studies are likely to have resulted in rapid coagulation of the ultrafine particles onto the accumulation mode. Therefore, it is possible that the particles inhaled by the experimental animals were only the larger (about 0.2 ：m) accumulation mode particles. Rapid coagulation of the ultrafine particles at several mg/m^3 of diesel exhaust can be assumed from homogeneous and heterogeneous coagulation processes (Hinds, Aerosol Technology, John Wiley, New York, 1982), and heterogeneous coagulation can be one to several orders of magnitude greater than homogeneous coagulation (NRC, 1979). Furthermore, depending on the time and site of cooling of the hot gases in the dilution tunnel to room temperature could lead to significant quenching of ultrafine particles.

The chemical composition of the accumulation mode and the ultrafine mode particles of diesel exhaust are probably quite different (Kittelson, D.B. and Watts, W. Nanoparticle emissions from engines. In: Nanoparticles: Applications in Materials Science and Environmental Science and Engineering. Natl. Science Foundation, p. 17-21, 2000; ISSN 1436-509X), which could be another important difference between the experimental animals *vs*. humans. The chemical composition of DPM described in this document (Chapter 2) is derived from filter samples with collection of both particle modes. They consist of elemental and organic carbon compounds. In fact it is stated in Chapter 2 that elemental carbon is the major component of diesel exhaust, contributing approximately 50-85% of the diesel particulate mass. In contrast, newer studies using particle size selective sampling show that ambient ultrafine particles consist mainly of organic carbon compounds. (European Aerosol Conference 2000; Hughes *et al*., *Environ. Sci & Technol*. **32**, No. 9, 1998). If ultrafine diesel particles as part of the ambient nuclei mode also consist of organics, this would point to an important difference between low environmental exposure of humans to diesel (ultrafine + accumulation mode particles) and high experimental exposures of rats to diesel (only accumulation mode particles). Although speculative, this suggested difference could be included into this document together with other hypotheses about differences in response to diesel between rats and humans

(*e.g.*, Section 7.4.5 - Integrative Hypothesis for Diesel-Induced Lung Cancer). Ultrafine particles (~20 nm) have a very high predicted deposition efficiency in the alveolar region of the respiratory tract, in fact per unit surface area they have an approximately fifty times higher deposition in the conducting airways compared to the alveolar region (ICRP 1994 model), and deposition is significantly greater than for accumulation mode particles. Significant differences of exposures of target cells between humans and rats may, therefore, occur at low and high exposure levels.

Some specific comments on Chapter 9 include: Avoid the use of microns, it should be micrometer (page 9-2, lines 27-28).

Page 9-12, lines 27/28: I suggest to add that the mutagenicity assays were performed at very high doses.

Page 9-17, line 25: Change microgram to milligram.

With respect to reaching closure of this Health Assessment Document for Diesel Exhaust, I am in favor of it, with the strong recommendation that EPA staff includes the changes that were discussed and agreed upon at the CASAC meeting on October 12/13, 2000.

Ronald E. Wyzga, Sc. D.

Overall Comments:

The document is much improved over earlier documents. The document is well organized, well written, and works systematically to a logical conclusion. During the course of the meeting, several changes were recommended for the document. Unfortunately, there was no record of the changes to be made. If the document incorporates the changes and caveats that my colleagues and I suggested, I believe that the document is ready for public release.

Chapter 1:

Executive Summary. Comments reflect those given below. I will bring specific comments to meeting.

Chapter 2:

This chapter is missing several recent references; they should be reviewed and incorporated into the document:

Brown, J. E.; Clayton, M. J.; Harris, D. B.; King, F. G., Jr. (2000) Comparison of the particle size distribution of heavy-duty diesel exhaust using a dilution tailpipe sampler and an in-plume sampler during on-road operation. J. Air Waste Manage. Assoc. 50: in press.

Christoforou, C. S.; Salmon, L. G.; Hannigan, M. P.; Solomon, P. A.; Cass, G. R. (2000) Trends in fine particle concentration and chemical composition in southern California. J. Air Waste Manage. Assoc. 50: 43-53.

Coburn, T. C. (2000) Statistical analysis of on-road particulate matter emissions from diesel vehicles. Inhalation Toxicol. 12(suppl.): 23-33.

Janssen, N. A. H.; de Hartog, J. J.; Hoek, G.; Brunekreef, B.; Lanki, T.; Timonen, K. L.; Pekkanen, J. (2000) Personal exposure to fine particulate matter in elderly subjects: relation between personal, indoor, and outdoor concentrations. J. Air Waste Manage. Assoc. 50: 1133-1143.

Kinney, P. L.; Aggarwal, M.; Northridge, M. E.; Janssen, N. A. H.; Shepard, P. (2000) Airborne concentrations of PM2.5 and diesel exhaust particles on Harlem sidewalks: a community-based pilot study. Environ. Health Perspect. 108: 213-218.

Ramadan, Z.; Song, X.-H.; Hopke, P. K. (2000) Identification of sources of Phoenix aerosol by positive matrix factorization. J. Air Waste Manage. Assoc. 50: in press.

Singh, R. B.; Huber, A. H.; Braddock, J. M. (2000) Development of a microscale emissions factor model for particulate matter (MicroFacPM) for predicting real-time motor vehicle emission. Presented at: PM2000: particulate matter and health--the scientific basis for regulatory decision-making, specialty conference & exhibition; January; Charleston, SC. Pittsburgh

The article by Christoforou et al. documents the nature of the changes in exposure that are occurring over time. These data would be important to include in the document, especially in section 2.2.8.1.3.

The paper by Kinney et al. shows that under some circumstances short-term exposures to diesel particles can be high.

Other comments:

The nature and significance of exposure patterns should be highlighted in the report. I realize that data are limited here; it would be useful for the document to emphasize the need to develop data to give us a good understanding of the magnitude and nature of personal exposures to diesel exhaust.

Chapter 5:

First of all this chapter is missing several key references:

Abe, S.; Takizawa, H.; Sugawara, I.; Kudoh, S. (2000) Diesel exhaust (DE)-induced cytokine expression in human bonchial epithelial cells. Am. J. Respir. Cell Mol. Biol. 22: 296-303.

Baeza-Squiban, A.; Bonvallot, V.; Boland, S.; Marano, F. (1999) Airborne particles evoke an inflammatory response in human airway epithelium. Activation of transcription factors. Cell Biol. Toxicol. 15: 375-380.

Donaldson, K. (2000) Nonneoplastic lung responses induced in experimental animals by exposure to poorly soluble nonfibrous particles. Inhalation Toxicol. 12: 121-139.

Green, F. H. Y. (2000) Pulmonary responses to inhaled poorly soluble particulate in the human. In: Gardner, D. E., ed. ILSI Risk Science Institute Workshop: The Relevance of the Rat Lung Response to Particle Overload for Human Risk Assessment; March, 1998. Inhalation Toxicol. 12: 59-95.

Kilburn, K. H. (2000) Effects of diesel exhaust on neurobehavioral and pulmonary functions. Arch. Environ. Health 55: 11-17.

Mauderly, J. L.; Bice, D. E.; Cheng, Y. S.; Gillett, N. A.; Henderson, R. F.; Pickrell, J. A.; Wolff, R. K. (1989) Influence of experimental pulmonary emphysema on toxicological effects from inhaled nitrogen

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All of the above should be incorporated into the document. I don't believe that any of them would dramatically change the conclusions or even tone of the report. They could, however, lead to a greater discussion of the relationship between diesel particle and PM health effects. Although this is discussed in the report, the discussion is rather superficial. The report should delve into issues, such as, is there reason to believe that diesel particles are as, more, or less toxic than PM generically. What health effects are seen for PM? and diesel particles? Have studies looked at the same endpoints for both groups? Were the results similar? What experiments need to be done to examine the role of the diesel particle fraction in PM health effects? I believe there is a general disconnect between these two mixtures: diesel emissions have generally been related to carcinogenic and chronic endpoints; PM, in general, has generally been linked to acute endpoints, especially mortality and cardiovascular endpoints. I believe that there is a need to examine the role of diesel emissions in some of the endpoints identified as being associated with PM exposures.

In the tables, I would like to see exposure levels broken down into the components of C x T. It would be interesting to examine other metrics besides the product of Haber's law to see if other patterns might emerge.

Chapter 6:

The discussion of the development of the PM-2.5 NAAQS misses the key issues as far as diesel particles are concerned. See my comments on Chapter 5. In many ways I believe that this section would be more appropriately placed in Chapter 5 than in Chapter 6, which should focus on the quantitative dose-response estimation. Given the lack of parallel studies for diesel exhaust and PM, I have probIems with statements, such as those on p. 6-17, stating that "the congruence of estimates attests to the reasonableness of data used and the judgments made in the RfC process…." I believe the similarity in numbers is due to coincidence.

Otherwise the material in this chapter is presented in a straightforward and logical approach that is consistent with EPA methods for calculating the RfC.
I have no major problem with the chapter as written. Perhaps the rationale for choice of the uncertainty safety factors could be clarified.

I would argue, however, that the toxicological database for DE may not be "relatively complete". P. 6-16, l. 25. The PM literature suggests that peak exposures are associated with a variety of health responses, some of which have not been thoroughly investigated for DPM. (See above comments on Chapter 5.) Studies, which examine the relationship between some of these responses (e.g., heart rate variability, other cardiovascular parameters) and peak DPM exposure should be encouraged. The RfC is concerned largely with chronic exposures; there could be a need to say something about the relative safety of acute exposures; it is my understanding that such a measure is under development; at some point, this measure could be applied to diesel emissions.

Chapter 7:

This chapter presents the key studies in a clear and consistent manner. There are areas where elaboration could be helpful. For example, there is scant discussion on p 7-19 on the Crump et al. and CalEPA analyses. This should be expanded to highlight the differences. I also believe that the Health Effects Institute held a workshop to help resolve the differences in these studies. The discussion of the difference in these two studies is more appropriate here than in Chapter 8, which should focus on the development of dose-response relationships. Since these studies received greater attention in other reviews, e.g., that of the State of California, it is important that they be fully discussed here so that the reader realizes that they were fully considered here.

On page 7-110 it could also be noted that the epidemiology literature considers exposures to diesel emissions from older technologies. It should be noted that there could be a difference in the carcinogenicity associated with the older technologies may or may be the same for the newer technologies. The emissions characteristics are different, and until studies are done on these technologies, it is difficult to make any judgment.

Chapter 8:

I agree with the Agency's decision not to derive a unit risk estimate for diesel exhaust. In addition to the arguments given here, I would add that we are dealing with a complex mixture, the composition of which is changing over time.
Hence it is unclear whether a unit risk estimate derived from specific conditions of exposure (pattern of exposure and composition of DE) could be extrapolated to different conditions of exposure.

I have a great many concerns about Section 8.4. I believe the perspectives can articulate societal concerns about DE and cancer without a fixed number, which can be easily misinterpreted and misused. Since numbers will be retained, I believe that all of the caveats associated with them should be highlighted and that there should be an explicit statement in the report which states: The risk numbers presented here are done so to help place the exposures to diesel emissions in perspective compared to other exposures. The risk numbers are highly uncertain for the many reasons given below. Accordingly these number should **not** be used to estimate the numbers of cancers associated with diesel emissions. Such numbers would be misleading. The estimates are based upon the following assumptions: 1.) there is an association between exposure to diesel emissions and lung cancer; 2.) the underlying dose-response relationship between exposure and cancer incidence is linear; 3.) the risk estimates involve using data from occupational studies, where the influence of smoking is unclear and where exposures have not been measured quantitatively; 4.) study exposures are tied to older technologies; current exposures probably reflect a mix with some emissions from newer technologies, which have not been evaluated; 5.) risk numbers are derived using methodologies designed to be protective; hence they may be an upper bound; for any one individual, the risk may be zero. On the other hand, the upper range of some public exposures to diesel emissions exceeds the lower range of occupational exposures which have been related to excess lung cancers.

Specific comments: Can the exposure levels in Table 8-1 be augmented to provide some idea of the year during which these exposures occurred? I raise this for two reasons: 1.) it may give some idea of exposure trend; 2.) it gives us some idea of how we may have to compensate for differences in DE composition over time as we learn more about these differences

Chapter 9:

This chapter appears to have two objectives: summarize all that was presented earlier and then interpret the conclusions made by the document. The document fairly accomplishes the first objective; I would like to see further clarification and caveats associated with the second objective, particularly in the document's hazard characterization of carcinogenicity. The document mentions the changing character of DE over time and notes that the evidence for carcinogenicity is largely tied to older technologies (some of which still exist in the real world, and many of which exist in the less developed world.) The key issue is the extent to which we can extrapolate across technologies. We just don't know, and it is important to articulate that fact. Hence whenever it is stated that DE is a probable human carcinogen, the statement should be caveated that the statement is based upon studies in which exposures to DE were tied to older

technologies. The extent to which this statement is true for technologies which have been introduced recently is unknown. I would add such a statement to section 9.4.2.2.5 and 9.5.2.

I also have some problems with section 9.5.1.. Given the disparity of the information used to derive the PM-2.5 standard and the RfC, I find it difficult to make the comparisons made here. (Incidentally the units on p. 9-17, l.25 should be mg not ug.) I also do not agree with the confidence of the RfC assessment is "medium". First of all, I don't know how to define "medium"; secondly until we have more data from more experiments, including more studies with humans, with different exposure patterns and at dose levels closer to ambient exposures, we have considerable uncertainty. I would drop line 31 on p. 9-17.

I'm also uncomfortable with the discussion beginning line 32,, page 9-20 through line 13, page 9-22. The document fairly summarizes what is know, wisely rejects the temptation to quantify in the face of great uncertainties, and makes a coherent and logical argument on how to characterize the carcinogenicity of DE. Why deviate from this practice here. We have large uncertainties about the exposure levels in the studies of concern; moreover the nature of exposures (patterns and composition of DE) are different in the studies and in the public domain. See my comments on Chapter 8.

Appendix C:

I am disappointed with this appendix. I had hoped to see some discussion of the linkages between PM and DE and what is know about their health effects.

Leslie Stayner, PhD

Chapter 6: Quantitative Approaches to Estimating Human NonCancer Health Risks of Diesel Exhaust

My only major concern with this chapter was the justification for dropping the use of an uncertainty factor for the interspecies extrapolation. In my comments on the previous draft of this document, I expressed a concern that EPA had only used a safety factor of 3 for interspecies extrapolation rather than the conventional factor of 10. The rationale given for this was that a pharmacokinetic (PBPK) model was used, and thus this removed the uncertainty related to species differences in kinetics that was assumed to be a factor of 3. However, this logic presumes that there is no uncertainty in the PBPK model, which is clearly not the case for the Yu model for reasons that are now discussed in the document.

I was therefore quite surprised when I found that this current draft not only dropped the factor of 3 for pharmacokinetics, but also dropped the other factor of 3 for pharmacodynamics. The rationale for dropping the factor for pharcodynamic differences was that rats were more sensitive to the non-cancer health effects of diesel exhaust exposure than humans. This statement was unreferenced, but appears to be in part based on a misinterpretation of an ILSI report. This report did draw this conclusion for lung cancer, but not for non-malignant respiratory diseases which is the health outcome in this analysis. It also appears to be based on a discussion in Chapter 3 of the histology findings of the NIOSH 2-year coal dust/DEP study in rats and primates (at exposures equivalent to the PELs; Lewis et al. 1989). Nikula et al. (1997) used tissue sections from the Lewis et al. study to compare particle retention patterns in rat and primate lungs (and found retention was primarily in alveoli in rats, and in interstitium in primates). On page 3-16 it is noted that the alveolar response was more severe in the rats, while the interstitial response was greater in the monkey; yet it is concluded that the rat is more sensitive. MOST IMPORTANTLY, this document and Nikula et al. ignore the fact that the rats were exposed for nearly a full lifetime, but the primates were exposed for only a fraction of their lives.

I was quite satisfied when the decision was made at our meeting to restore the factor of 3 for pharcodynamic differences, but still believe that there is some uncertainty related to pharmacokinetic differences. Of course, it would be difficult to argue on scientific grounds for a factor of 10 or 3 and this is probably a policy call. I do believe the resulting RFC value of
5 : g/m^3 should be reasonably protective of public health.

Other Comments

I agree with the decision to change the level of confidence in the RFC to medium, in the sense that I am reasonably confident that exposure to this level will not present a substantial risk of non-malignant respiratory diseases in the general public.

In discussing the use of the PM2.5 standard as an alternative means of justifying an RFC, it should be stressed that this level of exposure may still be associated with a substantial risk. If possible, it would be useful to present an estimate of risk for PM2.5 at the 15 ∶g/m^3 level to illustrate this point. I definitely agree with the decision to drop the analysis based on source apportionment, which was confusing, and based on an unsupportable assumption that diesel exhaust is responsible for all of the health effects associated with PM2.5 exposure.

We continue to have some concerns about the adequacy of the Yu model for predicting human doses, based on the work of Kuempel et al. (2000) in coal miners. If our experience with studies of coal miners applies to diesel exhaust exposed workers, then the Yu model would grossly underestimate the doses in humans at environmental exposure levels. The suggestion that was made by Dr. McClellan to consider using the ICRP and NCRP models as an alternative for humans seems very appropriate.

Page 614, 3rd para, 2nd sentence - Why would this assessment be for individuals of average health in their adult years. Doesn't EPA generally consider sensitive subpopulations in their assessments (e.g. the young and elderly)? The factor of 10 that was used for intra-human variability would seem to at least in part be used to address this concern.

Page 614, last sentence - This statement should be dropped for the reasons discussed above.

Chapter 8: Dose-response Assessment: Carcinogenic Effects

The revisions of this chapter are entirely consistent with concerns raised in the review of the previous draft of this document. In particular:

1. The revised document moved the review of previous risk analysis from the main body of the report to the Appendix, and deleted the table summarizing these risk estimates. This was in response to the comments from some of the reviews and public comments of the previous draft. The chapter simply states that "Appendix D provides a summary review of dose-response assessments conducted to date by other organizations and investigators." I think this chapter should at least briefly summarize these previous efforts and refer the reader to the Appendix for further information.

2. The document suggests that it is not possible to perform a dose-response analysis and therefore to develop a unit risk at this time based on the epidemiologic studies of railroad workers or truck drivers. I agree with this position, although hopefully the situation will be improved in the near future. We have been working with staff of the Office of EPA Mobile Sources to improve the estimates of historic diesel exhaust particulate exposures in the NIOSH study of teamster workers. We expect that this effort will result in significant improvements in our confidence in dose-response analyses using this study, although substantial uncertainties in exposure will certainly remain. We are also working collaboratively with Dr. Eric Garshick on the update of his study of railroad workers, and this may also help to make this study more suitable for dose-response analyses.

3. A added a section to this draft that provides a "Perspective" on the significance of the cancer risk using a rather crude method for determining the bounds of the risk that would be consistent with the epidemiologic studies of workers exposed to DEP. This change was responsive to at least one of the CASAC reviewer's comments (myself). The analysis is based on the following assumptions: 1) a linear dose-response relationship,

2) that the estimate of relative risk (1.4) from the meta-analyses of the occupational studies is unbiased, and 3) that the range of exposures in the epidemiologic studies were between 4 and 1740 micrograms per cubic meter. Each one of these assumptions needs to be clearly stated in the document (which it is not currently the case for all of these assumptions), and I believe some discussion of the reasonableness of these assumptions is warranted. Personally, I believe that they are all fairly easy to justify, and I would offer the following arguments for this position.

Linearity

The past practice of EPA and other U.S. agencies has been to assume that the dose-response relationship was linear when there was an absence of evidence to the contrary. I believe clearly that this is the position we are currently in, which is that we simply don't know if the dose-response relationship is linear or not. The fact that we are uncomfortable with using the existing epidemiologic studies for a dose-response assessment clearly suggests that we can't say anything at this time about the shape of the dose-response curve based on these studies. Although it is true that we do not find an excess of lung cancer among coal miners who are clearly exposed to overload concentrations, I don't believe one should interpret this as indicating that there is a threshold for particulate exposures and lung cancer in humans. First of all, many of these studies are SMR studies which rely on comparisons with the general population. Smoking may negatively bias these studies, since coal miners are not permitted to smoke while working and thus may have lower background lung cancer risks than the general population. Furthermore, its not clear whether the mechanism of action of diesel exhaust in humans is related to overload as it appears to be in rats and its quite possible that it is instead related to the genotoxic activity of the poly aromatic hydrocarbons that are adsorbed onto the diesel particles.

The toxicologic studies are also clearly uninformative with respect to the question as to whether the dose-response relationship in humans for diesel exposure and lung cancer risk is linear or not. If we accept the argument that the rat studies are not useful for estimating lung cancer risk in humans, then obviously one can not use these studies to argue that there is a threshold or non-linear dose-response in humans.

The Validity of the Meta-Analysis Relative Risk Estimate

It is generally impossible in epidemiologic studies to fully exclude the possibility of confounding. It is, of course, possible that the true meta-relative risk in these studies should be larger, smaller or even one (i.e., no effect). The fact that EPA and others have concluded that the weight of the evidence is consistent with diesel exhaust particulate exposure being a human lung carcinogen would lead one to at least

accept that the true relative risk must be greater than one. Even if it were less than 1.4 this would not have a great effect on the range of risk estimates that EPA has presented in the draft assessment. For example, if the true relative risk were 1.2 this would only reduce the risk estimates by a factor of 2, which is hardly of any significance in this context. Thus overall, I would argue that a relative of risk of 1.4 is unlikely to grossly overestimate the risk, could be an underestimate and that although the true risk might be 0 that this unlikely.

Range of Exposures in the Epidemiologic Studies is Between 4 and 1740 ∶g/m^3

Ideally the estimates of exposure used in this analysis should reflect that probable range of average exposures for the cohort studies that were included in the meta-analysis. The range used by EPA is clearly too broad for the studies included in the meta-analysis, and I am particularly concerned about the validity of the upper end of the range (1740). EPA cites the HEI 1995 report for the range, and this appears to come from a statement in a paper by Watts on page 121 of the report. **This review includes exposure assessments of miners, which is the only occupational group with exposures as high as 1740 ∶g/m^3. However, both of the meta-analyses cited for the relative risk estimate of 1.4 excluded studies of miners from their meta-analyses. Thus the use of 1740 ∶g/m^3 as an upper bound estimate of exposures was clearly inappropriate.** The highest reported average exposure from the epidemiologic studies appears to be 191 ∶g/m^3, which is the level for hostlers in the railroad study by Garshick et al.

Other Minor Comments

Page 8-7, 2nd para, 1st sentence - I don't think its true to say that cohort studies are usually used for dose-response assessments. Nested case-control studies and even sometime population based case-control studies may be equally or more valuable.

Page 8-8, 2nd para, 3rd sentence - It is stated that "an ideal dose-response analysis would account for ages when exposure to DE began and terminated . . . using exposure intensity over age rather than cumulative exposure". I don't understand the logic here. Accounting for what age exposure began and terminated may or may not be important depending on whether these variables modify the dose-response relationship. Using exposure intensity may or may not result in a better model than using cumulative exposure. I don't understand what is meant by "exposure intensity over age".

Page 8-10, 2nd para, last sentence - I simply do not understand what the authors are trying to say here.

Page 8-13, 2nd para, last sentence - I don't believe that these sources of uncertainty impact this analysis in "opposite directions". The true dose-response could be either supra-linear, sub-linear or linear. The actual exposure levels for the exposures is clearly a gross overestimate as discussed above, and would lead to an underestimation of risk.