February 4, 2000

EPA-SAB-CASAC-00-004

Honorable Carol M. Bowner
Administrator
U.S. Environmental Protection Agency
401 M Street SW
Washington, DC 20460

Subject: Review of EPA's *Health Assessment Document for Diesel Emissions* (EPA 600/8-90/057D)

Dr. Ms. Browner:

The Clean Air Scientific Advisory Committee (CASAC) of EPA's Science Advisory Board, supplemented by expert consultants (together referred to as the "Panel"), met on December 1, 1999 to review the November 1999 draft document, *Health Assessment Document for Diesel Emissions* (EPA 600/8-90/057D), in a public meeting in Research Triangle Park, NC. 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 present draft. The determination of the Panel regarding the draft reviewed in the December 1, 1999 meeting is summarized below. The attached report describes the Panel's views in more detail, and contains its responses to the four specific questions posed by Staff as a charge to the Panel.

It was clearly apparent that Staff made a strong effort to respond to the Panel's earlier recommendations in developing the revised draft. The Panel compliments Staff for developing a draft that is a marked improvement over previous drafts, and which serves as an excellent platform for final revisions comprising an acceptable document. However, the number of major and minor remaining criticisms and recommendations raised by the Panel precluded closure on the document, which would assume no further review by the Panel of changes made in response to the Panel's comments.

The Panel agreed with the decision to not develop a quantitative estimate of human lung cancer risk from environmental exposures to diesel emissions in the present document. It may be possible to develop such an estimate following completion of ongoing efforts to improve understanding of exposure-dose-response relationships. CASAC looks forward to reviewing the results of any future Agency efforts to develop quantitative risk estimates for diesel emissions.

Although the combined weight of numerous issues precluded closure; the most intense discussion surrounded two especially critical issues. First, 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. The Panel disagreed with the use of allergenic responses should to derive the pharmacodynamic uncertainty factor for the hazard presented by the designated "critical effect", pulmonary histopathology. Although both effects may have inflammation in common as a precursor response, the Panel did not agree that the inflammatory response attributable to particle overload in the lung could be equated to inflammatory changes occurring during an allergenic response in the upper airways.

Second, the majority of the Panel disagreed with the Agency's use of the description "highly likely" to portray cancer hazard from environmental exposures. There was substantial disagreement with the use of the discretionary descriptor "highly" to modify the category "likely", in view of the continuing uncertainties in extrapolating occupational data to environmental exposure levels. The Panel viewed the uncertainties in occupational exposure-response relationships as important in judging cancer hazard, as well as quantitative risk, at environmental exposure levels.

In summary, the Panel recognized the document as a considerable improvement over previous drafts, but could not close on the document in view of remaining concerns. The Panel looks forward to the opportunity to review and approve an appropriately revised document. We look forward to your response to the advice contained in this report.

Sincerely,

/signed/
Dr. Joe L. Mauderly, Chair
Clean Air Scientific Advisory Committee

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U.S. Environmental Protection Agency
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1. EXECUTIVE SUMMARY

The Clean Air Scientific Advisory Committee (CASAC) of EPA's Science Advisory Board, supplemented by expert consultants (together referred to as the "Panel"), met on December 1, 1999 to review the November 1999 draft document, *Health Assessment Document for Diesel Emissions* (EPA 600/8-90/057D), in a public meeting in Research Triangle Park, NC. This review followed a review of the previous draft in May, 1998, and a consultation between the Panel and NCEA Staff (hereafter referred to as "Staff") on June 10, 1999 regarding the development of the revised document.

The draft reviewed by the Panel was considerably improved over previous drafts. The Panel complimented Staff for its strong effort to revise the document in accordance with the Panel's previous comments and recommendations. The Panel approved of the framework of the present document and the general approach taken to portraying key information. However, the number of major and minor criticisms and recommendations raised by the Panel during the review precluded closure on the document without further review of changes made in response to the Panel's comments.

No single issue precluded closure; rather, the combined weight of numerous major and minor issues contributed to the need for revision and re-review. However, much of the discussion surrounded two critical issues. First, there was substantial concern for the approach taken to deriving the uncertainty factors used in calculating the RfC value for noncancer health effects. The Panel did not disagree strongly with the use of pulmonary histopathology as the "critical effect" for calculating the RfC, but it did disagree strongly with the use of a different effect, allergenic responses, to derive the pharmacodynamic uncertainty factor for the hazard presented by the critical effect. The panel did not agree that these two effects were sufficiently similar or had sufficiently common underlying mechanisms to warrant their combined use in this manner.

Second, there was also substantial disagreement with the use of the descriptor "highly" to modify the category "likely" used to describe the potential human carcinogenicity of environmental exposures to diesel emissions. The majority of the Panel did not agree that the current level of confidence regarding the exposure-response relationship from occupational exposures warranted the discretionary use of the term "highly" to describe the confidence regarding the cancer hazard from environmental exposures. The Panel agreed with the Agency's judgement that a quantitative estimate of unit risk for human lung cancer from environmental exposures to diesel emissions could not be made with an adequate level of confidence at this time, and viewed the source of that lack of confidence as also conflicting with the characterization of hazard as "highly likely".

In summary, the Panel recognized the document as a considerable improvement over previous drafts, and is encouraged that, after revisions responding suitably to the remaining concerns, the document could be approved as an acceptable representation of current knowledge on the potential health effects of diesel emissions. The Panel looks forward to closing on an appropriately revised

document, and to reviewing the results of future efforts to derive a quantitative estimate of unit human lung cancer risk.

2. INTRODUCTION

2.1 Introduction

The Clean Air Scientific Advisory Committee (CASAC) convened a Diesel Review Panel (Members plus expert Consultants) to conduct a review of the Agency's revised draft Health Assessment Document for Diesel Engine Emissions (EPA, 1999) prepared by the Agency's National Center for Environmental Assessment (NCEA) - Washington, DC Office. The Committee met December 1, 1999 in Research Triangle Park, NC.

This effort follows earlier reviews, the first in 1995 when CASAC conducted a peer review of the December 1994 version of the 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).

More recently, CASAC reviewed the 1998 draft of the diesel assessment 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 made by CASAC in 1995. The CASAC Diesel Review Panel that was created for this 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).

2.2 Charge

The Agency's review of the CASAC October 1998 report, and of more recent literature since February 1998, formed the basis for several changes to the 1999 draft Health Assessment for Diesel Emissions and refined the issues for which the CASAC's advice would be helpful as the Agency finalizes the assessment. Several of these issues were discussed in consultation with the CASAC in June 1999 (see CASAC, 1999). Charge to the CASAC Reviewers

a) A CASAC concurrence that we have adequately updated the requested topics and reasonably characterized related key findings, if any, would be welcomed. The CASAC's past expertise on emissions is a particularly helpful aspect since this topic seems to have only limited information that can be used to understand the trends in emission changes over the years. If we have missed anything that is pivotal information, we would like to be made aware of it.

b) The draft assessment characterizes diesel emissions as posing a "highly likely" or "probable" lung cancer hazard to humans, and that it is prudent to view the hazard as being present at environmental levels of exposure. Is our explanation of the scientific plausibility of the environmental hazard reasonable?

c) The topic of dose-response (leading to cancer unit risk or potency derivation) is the most contentious portion of the draft assessment's characterization of potential diesel emissions exposure health effect outcomes. We have declined, for the time being, to reiterate old dose-response debates about the railroad worker data, preferring to await the availability of mortality updating this study. In addition, we have chosen not to characterize quantitatively potential risk until we can carry out an examination of postulated uncertainties in the 1998 Teamster Union Truck Driver risk assessment. We intend to do this work in collaboration with our colleagues at the National Institute for Occupational Safety and Health. Does the CASAC concur with this "wait and see" approach? Given that the outcome of this draft assessment is to characterize a likely human carcinogenic hazard, does the CASAC have a suggestion for a way, other than what has been offered in the assessment (i.e., Chapter 8 and Chapter 9), to provide a perspective about the possible magnitude of risk levels, short of presenting a highly uncertain unit risk?

d) We have attempted to discuss the linkage between ambient PM and diesel-specific PM. There are emissions, exposure and health effect findings to compare, with both similarities and differences to note. A direct numerical comparison of the PM2.5 health criteria and resulting standard to the diesel emissions noncancer respiratory effects reference concentration (RfC) is more complex and has not been done. Does the CASAC feel that the linkage discussions in the various chapters is adequate to address their earlier stated concern?

3. DETAILED COMMENTS

3.1 Response to the Charge

The November 9, 1999 letter to the CASAC Chairman from Dr. William Farland of NCEA transmitting the draft health assessment document for review contained an enclosure listing a four-point charge to solicit the Panel's opinion on specific issues. These points and the Panel's summary responses are listed below. These issues were discussed with Staff at the meeting, and are addressed in more detail in subsequent sections and the appended material.

3.1.1 Adequacy of Updating key Information

> *"A CASAC concurrence that we have adequately updated the requested topics and reasonably characterized related key findings, if any, would be welcomed. The CASAC's past expertise on emissions is a particularly helpful aspect since this topic seems to have only limited information that can be used to understand the trends in emissions changes over the years. If we have missed anything that is pivotal information, we would like to be made aware of it."*

The information presented in the document was markedly improved over the last draft by the updating done by Staff. Chapter 2 (emissions) was especially improved, allowing the present review to focus largely on "fine tuning" the information presented. The Panel's recommendations for further improvement in the final draft included some, but not many, suggestions for updating information. The Panel's comments at this review focused more on the need to treat certain topics more thoroughly, than on the need to cite more updated information.

3.1.2 Characterization of Environmental Cancer Hazard

> *"The draft assessment characterizes diesel emissions as posing a 'highly likely' or 'probable' lung cancer hazard to humans, and that it is prudent to view the hazard as being present at environmental levels of exposure. Is our explanation of the scientific plausibility of the environmental hazard reasonable?"*

The characterization of environmental cancer hazard is perhaps the most important issue in the document, and was accordingly a major topic of discussion. The majority of the Panel did not agree with the characterization of environmental lung cancer risk as "highly likely". The Panel did not argue strongly against the conclusion that a cancer hazard was likely associated with historic occupational exposures. When questioned at the meeting, Staff stated explicitly that they intended the characterization "highly likely" to extend to environmental, as well as occupational, exposures. The use of the modifying descriptor "highly" was not considered by most of the Panelists to be consistent with

the current level of confidence that a significant cancer hazard exists at current environmental exposure levels.

3.1.3 Deferral of Quantitative Estimate of Cancer Risk

> *"The topic of dose-response (leading to lung cancer unit risk or potency derivation) is the most contentious portion of the draft assessment's characterization of potential diesel emissions exposure health effect outcomes. We have declined, for the time being, to reiterate old dose-response debates about the railroad worker data, preferring to await the availability of mortality updating this study. In addition, we have chosen not to characterize quantitatively potential risk until we can carry out an examination of postulated uncertainties in the 1998 Teamster Union Truck Driver risk assessment. We intend to do this work in collaboration with out colleagues at the National Institute for Occupational Safety and Health. Does the CASAC concur with this 'wait and see' approach? Given that the outcome of this draft assessment is to characterize a likely human carcinogenic hazard, does the CASAC have a suggestion for a way, other than what has been offered in the assessment (i.e., Chapter 8 and Chapter 9), to provide a perspective about the possible magnitude of risk levels, short of presenting a highly uncertain unit risk?"*

The Panel agreed that it was not appropriate for the Agency to develop a quantitative estimate of human lung cancer risk at this time. The Panel did not agree with the exclusion of a description of previous reanalyses by Crump, Dawson, and the Health Effects Institute (HEI). The Panel suggested that the document contain a more explicit description of the ongoing effort thought likely to improve the Agency's ability to develop a quantitative risk estimate with an acceptable level of confidence. Although individual Panelists offered suggestions regarding portrayal of cancer hazard in this document, no consensus advice emerged. The Panel looks forward to reviewing the results of future efforts to derive a quantitative estimate of human lung cancer risk.

3.1.4 Adequacy of Linkage to Ambient PM

> *"We have attempted to discuss the linkage between ambient PM and diesel-specific PM. There are emissions, exposure, and health effect findings to compare, with both similarities and differences to note. A direct numerical comparison of the $PM_{2.5}$ health criteria and resulting standard to the diesel emissions noncancer respiratory effects reference concentration (RfC) is more complex and has not been done. Does the CASAC feel that the linkage discussions in the various chapters is adequate to address their earlier stated concern?"*

The Panel acknowledges the difficulty of dealing with the linkage between diesel particulate material (DPM) emissions and ambient PM on the basis of current knowledge. It also acknowledges

the efforts of Staff to improve discussions of the linkages in the revised document. However, the Panel continued to note several places throughout the document in which the linkage discussions still need to be strengthened. An explicit, rational case for dealing with DPM differently than with ambient PM (of which it is virtually always a subset) has not yet been adequately stated. It is reasonable, for example, to question whether the Agency can justify setting the reference concentration (RfC) for DPM at one-third the annual ambient PM standard on the basis of a known greater potency of DPM than total ambient PM in eliciting the critical health effect. In the absence of direct comparisons of health outcomes, the case would have to be based on the compositions of DPM and ambient PM regarding the compound(s) thought to elicit the effect(s). Overall, discussion of the linkages between health hazards from DPM and the combination of DPM and other ambient PM still needs strengthening.

3.2 Comments by Chapter

Only a summary of the key points raised by the Panel is given below, to indicate the general nature of the remaining concerns. Many more general and specific points are raised in the individual written comments of the Panel Members, which are appended to this report. CASAC encourages Staff to review all of the attached comments and the transcript of the discussion at the meeting in order to take the full advice of the Panel into consideration in revising the document.

3.2.1 Chapter 1: Executive Summary

This chapter will need to be revised to reflect changes made in subsequent chapters.

Care should be taken in describing the relationship between diesel particulate matter (DPM) and ambient PM to recognize that DPM is a ubiquitous subset of ambient PM, and is no more different from ambient PM than the contribution from any other specific source. As a related issue, the assertion that elemental carbon is "nearly unique" to DPM is an overstatement in view of information given in the next chapter.

The specific health effect serving as the basis for calculating the RfC should be stated.

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

This chapter does not yet deal adequately with the exposure profile of the general public to diesel emissions. A better treatment is needed of the distributions of ambient DPM concentrations, the distribution of personal exposures, the magnitude of differences between typical peak and average exposures, and the contribution of exposures in extreme high-concentration microenvironments to total exposures.

Better information on past, present, and projected future diesel emissions inventories would enhance the chapter, as would more information on the relationship between regulatory standards and actual in-use emissions.

The conclusion that diesel emissions, and thus probably their toxicity, have not changed appreciably over the years is not convincingly supported by the information in the chapter. For example, information is given suggesting that the organic fraction of DPM has decreased with time; thus, implying that health hazards associated with the organic fraction are also likely to have decreased. Because of the importance of this issue to subsequent conclusions, it needs to be dealt with more directly and clearly.

Some facets of the description of DPM need strengthening. The assertion that airborne elemental carbon is nearly unique to DPM appears to be an overstatement. The fact that DPM has not demonstrated hygroscopic growth should be stated. Because of the questions being raised about ultrafine DPM, Staff should ensure that the latest published information on the emissions and composition of ultrafine DPM are incorporated into the revision

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

The chapter needs to be reviewed carefully for correctness of terminology. The words "deposition" and "deposited" are used incorrectly in place of "retained' or "translocated" in several places. In some places, "dose" is used inappropriately in describing "concentration" or "exposure".

There are sections in which the reader has difficulty determining whether the author is talking about the entire DPM or only the elemental carbon core.

Information on the dosimetry of DPM could be better linked to information on dosimetry given in the PM Criteria Document, including a quantitative comparison of the expected deposited dose of DPM vs general ambient PM. Dosimetry in susceptible populations should be discussed, as it is in the PM Criteria Document. Rather than reproducing sections in the PM Criteria Document, these changes could be accomplished by summarizing key points and referencing the Criteria Document.

In addition to the Yu et al. deposition models used in this chapter, other models in current use should be cited (e.g., ICRP, NCRP). In order to place the estimates of deposition in context, there should be some mention of the range of estimated regional deposition efficiencies among the several models in current use.

The 1998 ILSI workshop should be referenced in regard to the overload issue.

3.2.4 Chapter 4: Mutagenicity of Diesel Exhaust

The Panel had previously recommended adding more discussion of current information on the mutagenicity of particles having little or no organic content, including evidence for the involvement of reactive oxygen species in mediating the effects of those particles. It had also been suggested that the high doses of particles and organic extract used in mutagenicity assays be placed in context relative to doses likely to occur from inhalation of diesel PM in the environment. Neither has yet been done adequately.

The work of Wallace et al. at NIOSH on the mutagenic activity of whole DPM should be cited.

3.2.5 Chapter 5: Noncancer Health Effects of Diesel Exhaust

The references to the various studies throughout the chapter need to be reviewed carefully to increase accuracy. In some cases, multiple reports from the same study appear to be cited as different studies, and a more integrated view of the information would be gained by noting the linkages among the reports. The descriptions of exposures and exposure concentrations are sometimes inaccurate or conflicting. There are measurements ascribed to studies in which the measurements were not made.

The linkage between the information in this chapter and information on the noncancer effects of general ambient PM, as described in the PM Criteria Document, still needs strengthening.

The chapter needs a better discussion of linkages between the noncancer findings in humans and those observed in animals. In some cases, such as the effect on allergenicity, the effects observed in experimentally-exposed humans are confirmed and strengthened by the animal studies. In other cases, such as fibrosis, emphysema, pulmonary hypertension, and cor pulmonale, it should not be implied that the evidence from heavily-exposed animals suggests that these effects would occur in humans at environmental, or even most occupational, exposure levels.

The discussion of the immunological and inflammatory changes lacks sufficient interpretation. The chapter correctly cites studies in which exposure-related changes either were or were not observed, but attempts little explanation of the differences among the study designs and endpoints that would explain the differences in results. This tends to leave the reader with a sense that the positive and negative findings somehow balance each other such that the end result is a lack of understanding. In fact, there is little conflict among the current data when the studies are properly interpreted in light of immunological mechanisms. The single case report of “diesel asthma”, which likely resulted from a high-dose irritant effect, should not be cited as an allergenic effect. Immunity, allergenicity, and inflammation are intimately interconnected, and this information needs a more analytical treatment.

3.2.6 Chapter 6: Noncancer Dose-Response Evaluation: RfC Derivation

This chapter would benefit greatly by the addition of an opening discussion describing the specific noncancer effect(s) the RfC is aimed at protecting against, and why the ambient PM standard

does not confer adequate protection against DPM. The chapter presently opens with a description of options and methods for calculating reference exposure values, but does not justify the effort or place it in context.

In reviewing the previous draft, the Panel noted the need for a more clear statement of the rationale for selecting an RfC that was different from the annual average standard for ambient PM. Although the issue is mentioned in the revised document, it was not considered to have been addressed as thoroughly or as convincingly as needed.

The rationale for why a benchmark dose analysis could not have been done was not considered to be very clear or convincing.

The method used to derive the RfC was described much more clearly in this draft than in the previous draft. Based on its clearer understanding of the method however, the Panel voiced serious concerns about the approach used.

The most serious concern was the use of allergenicity in deriving the pharmacodynamic (PD) uncertainty factor, when it was stated that pulmonary histopathology was to be the critical effect on which the RfC was based. While the Panel did not argue strongly against the use of pulmonary histopathology as the critical effect, it did not agree with the use of a different effect, allergenicity, to make the uncertainty adjustment. The Panelists having the most knowledge of the responses did not agree that these effects are linked, or that they necessarily have the same underlying mechanisms. Although both effects may have inflammation in common as a precursor response, the Panel did not agree that the inflammatory response attributable to particle overload in the lung could be equated to inflammatory changes occurring during an allergenic response in the upper airways. In addition, the case is made throughout the document that the carbon core of DPM is likely to be responsible for the pulmonary histopathology, while current information suggests that the organic fraction of DPM may be most closely linked to the allergenicity effect. Overall, the Panel was not convinced by the rationale presented for using a different health effect for the uncertainty factor.

It is stated that the rat appears more sensitive than humans to noncancer effects, and the Panel did not disagree with this interpretation of current information. If this is so however, it is not clear why an adjustment for uncertainty in PD is required at all.

Some concern was expressed for the assumption that the pharmacokinetic (PK) model eliminated uncertainty related to the interspecies difference in dose. Although current information suggesting potential inadequacy of the model adjustment is related to occupational dust exposures rather than exposures at environmental levels, the adequacy of the interspecies adjustment should be discussed more thoroughly.

The concept of "average lifetime exposure" is not defined unambiguously, and should be discussed more thoroughly. The present document does not make sufficiently clear why lifetime exposures should be more important than acute exposures for noncancer effects.

Considering the number and nature of the issues described above, the Panel was not assured that the RfC value presented in the document was appropriate, and was certainly not convinced that the RfC was attended by a "high level of confidence", as indicated in the document.

3.2.7 Chapter 7: Carcinogenicity of Diesel Exhaust

The approach to presenting the large number of human and animal studies was improved little over the last draft. The chapter would benefit from having a "road map" paragraph at the beginning of each section, followed by supporting detail. Tables should precede presentation of the individual studies. Several inaccuracies in the descriptions persist from the last draft. The individual Panelists' comments contain several suggestions for improvement of the discussion of both the human and animal data.

The section applying the "Hill" criteria to diesel emissions is problematic. If this section is to be included, the seminal reference by Hill should be cited, and the discussion should rely on the original criteria, rather than interpretations from secondary references. The claim that the diesel-cancer relationship fulfills the criteria is questionable. Regarding the "strength" criterion, it is claimed that the diesel-cancer relationship is "strong", but risk ratios of around 1.4 would in fact be characterized as weak. The rationale presented for compliance with the "specificity" criterion is questionable. Compliance with the "dose-response" criterion has not been demonstrated convincingly. The inclusion of a comparison to the Hill criteria is reasonable, but as presented in this draft, the section adds little to the document.

The issue of latency should be discussed more thoroughly in regard to the existing epidemiological data and analyses. Confidence in the study findings portrayed in the chapter is lessened by the relatively limited length of both exposure and follow-up.

The rationale for excluding "hypothesis generating" studies is not convincing.

This chapter does not deal with the reanalyses of the railroad worker data done by Crump and Dawson. This issue is alluded to in the next chapter, but is not described well anywhere in the document. Staff should include a more thorough treatment of this issue, either in this chapter or the next. At the review of the last draft , the Panel recommended that these reanalyses be described, or at least summarized, in order to portray the difficulty in estimating the carcinogenicity of diesel emissions from the current epidemiological data. The HEI reanalysis should also be described. The fact that this draft does not include a quantitative estimate of cancer risk does not preclude the usefulness of

discussing these reanalyses more thoroughly. Indeed, the information supports the Agency's decision not to estimate cancer risk at this time.

Although there was mixed opinion regarding the characterization of diesel emissions as "highly likely" to be a human carcinogen, the majority of the Panel did not agree that there was sufficient confidence (i.e., evidence) to use the descriptor "highly" in regard to environmental exposures.

3.2.8 Chapter 8: Cancer Dose-Response Evaluation

The Panel agreed with the Agency's decision to defer quantitative estimates of cancer risk at this time. In view of the inability to portray unit risk with acceptable confidence based on current information, several panelists recommended deletion of the table listing historical estimates of unit risk.

The Panelists offered a range of views regarding approaches to describing the potential nature and magnitude of cancer risk in humans, and the relevance of the animal data in supporting the existence of cancer hazard. No consensus recommendation emerged, other than to agree that a quantitative estimate of unit cancer risk should be deferred.

This chapter alludes to work that is ongoing and will be completed in the near future, which will improve the understanding of cancer risk and perhaps allow a quantitative estimate of cancer risk with acceptable confidence. In view of the importance and controversial nature of this issue, that ongoing work should be described.

As stated above, the majority of the Panel did not agree with the use of the descriptor "highly likely" to describe the carcinogenic potential of environmental exposures of humans to diesel emissions.

3.2.9 Chapter 9: Characterization of Health Hazard and Dose-Response for Diesel Engine Exhaust

This summary chapter was viewed as very useful, and the general approach to its development was viewed as appropriate. The Panel encourages Staff to focus on its readability by a broad audience when making the final revisions. Some technical jargon carried over from the previous chapters should be eliminated, and care should be taken to avoid introducing information, concepts, or terms that were not contained in previous chapters.

Because of the summary nature of this chapter, the issues raised during its discussion were largely identical to those raised in the previous chapters. Although several issues and suggestions are presented in the individual Panelists' written comments, the two issues generating the most energetic discussion were: a) the derivation of the RfC; and b) the use of the descriptor "highly" together with the categorization "likely" in regard to cancer hazard from environmental exposures.

4. CONCLUSIONS

Although not unanimous, it was the summary view of the Panel that it could not close on the document without reviewing changes made in response to the issues described above. Overall, the document clearly demonstrated a strong effort by Staff to respond to previous criticisms and advice, and the Panel complimented Staff for marked improvements in most sections.

No single issue precluded closure; rather, numerous major and minor issues contributed to the aggregate need for revision and re-review. However, much of the discussion surrounded two issues. First, there was substantial concern for the approach taken to deriving the uncertainty factors used in calculating the RfC value for noncancer health effects. Specifically, the Panel was not convinced of the appropriateness of using allergenic responses to derive the pharmacodynamic uncertainty factor for the hazard presented by the "critical effect", pulmonary histopathology. Second, there was substantial disagreement with the use of the term "highly" to modify the category "likely" used to describe the potential human carcinogenicity of environmental exposures to diesel emissions. Specifically, the majority of the Panel did not agree that the current level of confidence regarding cancer hazard from environmental exposures supported the discretionary use of the term "highly". The Panel agreed with the Agency's judgement that a quantitative estimate of unit cancer risk could not be made with an adequate level of confidence at this time, and viewed that lack of confidence as conflicting with the characterization hazard as "highly likely".

The Panel looks forward to closing on an appropriately revised document, and to reviewing the results of future efforts to derive a quantitative estimate of unit human lung cancer risk.

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

APPENDIX A -- INDIVIDUAL COMMENTS

The following are the original, unedited written comments provided by individual Panelists prior to or at the December 1, 1999 meeting. They do not reflect consensus of the Panel and, in some cases, may have been revised subsequent to the meeting as a result of discussion. They were provided to the Aqency following the meeting so that Agency staff would have detailed editorial comments as well as individual responses to the Charge. The material in this Appendix, along with the discussions at the December 1st meeting form the basis for this written report. (Note: these comments may contain uncorrected typographical errors that result from electronic translation).

Joe L. Mauderly

Summary Comments

This draft is much improved over the February 1998 draft, and clearly represents a serious attempt on the part of the Agency to respond positively to the last CASAC review. Staff are to be complimented on their effort to move significantly forward with this draft.

The decision to not make a quantitative estimate of unit risk for human lung cancer is a good one, and one that accurately reflects our current state of knowledge and confidence. I agree with the Agency that perhaps such an estimate might be made with acceptable confidence pending completion of ongoing efforts.

In view of the key criterion for acceptance - that the document be an accurate and complete representation of current knowledge on the health effects of diesel engine emissions - I believe that this revision comers very close to being acceptable. Numerous minor edits are needed, but I have only three major points of criticism.

First, the document still does not contain a clear evaluation of how changing emissions trends might or might not impact the health risks. It is clear that the Agency's position is that mass reduction is the only risk-related change, but this position is not well-defended. In summary information, it is stated that there has been little change in the ratio of organics to the total particle, yet that seems to conflict with information in Chapter 2. It is stated that the proportions of the "toxicologically significant" material, defined as PAHs and nitroaromatics, haven't changed, yet nowhere are these agents cited as the key toxicological components – especially for non-cancer effects. Chapter 5 doesn't point toward any key particle component for non-cancer effects, although it mentions several. Overall, the statements about the changes having no important impact on toxicity are not convincing as currently presented. I don't consider this issue to be resolvable on the basis of current knowledge, and I don't argue strongly with the Agency's "bottom lines". I do, however, believe that the issue could be treated more thoroughly and with less apparent conflict in statements than in the present draft.

Second, I do not understand the justification of the pharmacodynamic component of the uncertainty factor in calculating the RfC. The Agency states that its derivation of the RfC will be based on the critical effect of lung histopathology, and especially on the inflammatory and fibrotic responses. It states accurately that current expert opinion holds that the rat is at least equally sensitive, and perhaps more sensitive, than humans to the inflammatory/fibrotic lung response. It also states, again accurately, that our information on the allergenicity response is not yet solid enough to be used as a criterion for the RfC, even though it may someday become a justifiable basis. Yet in its derivation of the RfC, the Agency uses the allergenicity argument to justify its use of a cross-species adjustment in pharmacodynamics. As presently offered in the document, this strategy is not adequately justified and appears inappropriate.

Third, I do not agree that the qualifier "highly" should be used with the descriptor "likely" in portraying the cancer hazard. The term "highly" is not a key term in the new cancer risk guidelines; "likely" is sufficient there. The agency believes that there is sufficient uncertainty in our present understanding of the epidemiological data that it elects not to attempt calculation of a unit cancer risk estimate. Yet, the Agency feels that its level of confidence is sufficiently high to apply the term "highly" to the judgement that diesel exhaust is likely to be a human carcinogen. I might have accepted that, until the Agency stated clearly at the CASAC meeting that it intended the "likely" qualifier to apply to environmental, as well as occupational, exposures. Until the dose-response relationship is further defined, I do not agree with the use of "highly" in regard to cancer risk from environmental exposures.

Chapter-by-Chapter Comments

Chapter 1: Executive Summary

1-1, 23-24: First, elemental carbon is also emitted from gasoline engines, among other sources. While most properly-operating gasoline vehicles emit very little elemental carbon, poorly-operating ones emit much more. Because there are so many more gasoline vehicles than diesel, it doesn't seem quite accurate to say that elemental carbon is "nearly unique" to diesels. In Chapter 2, Section 2.4.2.2 clearly presents a picture different from the "nearly unique" description. Second, what does the statement mean that "DE gases are more ubiquitous in an urban environment"? There may be more sources of many, if not all, of the gases and vapors emitted from diesel engines than there are of carbon, but diesel-derived carbon is about as "ubiquitous" in the urban environment as you can get. Was there ever an area sample without it?

1-2, 8-10: This statement doesn't seem to reflect very accurately the information in Chapter 2 indicating a reduced organic fraction with time.

1-2, 12-16: First, the wording here doesn't seem to be quite right yet. First, it is not clear what is meant by "higher or at least highly varied". I think I know what you mean by mentioning "highly varied", but the wording isn't quite there yet. Second, noting similarities and differences "between DE and ambient PM" isn't quite right either. There are few, if any, ambient PM samples that don't contain DE particles. You should screen the text for any statement that seems to imply that diesel soot is not ambient PM.

1-2, 23-24: The basis (ie, the key effect) for the RfC should be stated in this summary. An assortment of effects is listed, but it should be stated which is the key determinant. This is especially important because it is a contentious issue whether or not you used lung responses as the key response, as stated later, or whether you are mixing responses.

1-4. 15: Change "ventilatory frequency" to "minute volume" or some such term. The breathing <u>frequency</u> has no importance here, as implied. It's the greater ventilation of the lung per unit of lung size in children that is the legitimate issue.

Chapter 2: Emissions

2-15, 1: I think you mean 4-stroke instead of 2-stroke.

2-32, 18: Because California is part of the U.S., it would be best to list the composition for California fuel as well, instead of just noting that it's different. After all, there may be more person-micrograms of exposure in California to on-road emissions than there is in the rest of the country from off-road emissions.

2-47, Section 2.2.6.1: Overall, the information on SOF vs. EC is confusing, and does not give the reader a bottom line. It is stated that both are declining, which is understandable and supported by the data given. It is also stated in different places that the SOF is declining as a portion of the total particle. Yet in other chapters, the conclusion is given that the ratio of SOF to EC has not changed over the years. It is not clear where that conclusion is supported in this chapter.

2-70, 12-20: This paragraph is redundant to material presented earlier in more detail.

2-82-85, Tables 2-17-20: The sources of data in these tables ought to be stated in the legends, or in footnotes, as done for other tables and figures in the chapter. The source is described in the text, but it is both customary and clearer to give that information in the table also.

2-87, 2-4: The issue of trends in SOF and EC with time appears to be properly stated and based on cited results. SOF has apparently declined as a portion of total particulate. However, here, and later in the document, the position is taken that the ratio of the "toxicologically significant" material, defined as PAHs and nitroaromatics, to the total particle has not changed. Considering at least that these materials may not cause the irritant (inflammatory) effects, and also that other compounds might be important for cancer, it seems a stretch to make this a blanket conclusion throughout the document. In Chapter 5, non-cancer toxicological effects are not ascribed to specific components, nor does the wording there suggest that PAHs and nitroaromatics are the key culprits.

Chapter 3 – Dosimetry

General Comments

1. The chapter is significantly improved in several ways:

    More balanced, incisive discussion of several points, including uncertainties
    Inclusion of discussion of POCK model

    Inclusion of portrayal of likely human doses of PAHs

2. The term "deposition" is used inappropriately in multiple locations, such as:

    3-7, 2

3-11, 7
3-23, 7-8
3-40, 13

The text should clearly differentiate when it is talking about the entire soot particle and when it is talking about only the carbon "core". There are conflicting statements about the solubility of the particles, and it appears as if the issue of carbon core vs. organics is confused. The hazard assessment is done for the entire particle mass, so it would be best to keep that definition consistent throughout the document.

Specific Comments

3-3, 32: Omit the comma after "particles". It changes the implication.

3-6, 1: Space between the first 2 words.

3-7, Table 3-1: The meaning or definition of the symbols in the footnotes can't be understood without referring to the paper cited.

3-7, 1: The meaning of this sentence isn't clear. "Alternative" to what? Haven't you been talking about deposition rate based on exposure concentration?

3-8, 1: In the statement about DPM being "insoluble", do you include the organics when you indicate that the dissolution rate is insignificant in comparison to the clearance half-time? In other places in the document, it is stated that organics do dissociate from the soot in the lung.

3-8, 6: What happens in the olfactory region?

3-10, 18, and hereafter in the chapter: There should be some consistency in citing the exposure levels. Throughout the document, both 7.0 and 7.1 mg/m^3 are used. Because the actual concentration was 7.08, 7.1 is more accurate. Although the interpretation is not affected, having two different concentrations for the same study might confuse readers into thinking that you were talking about different exposure groups.

3-11, 7: Particles are not "deposited" in the interstitium in the sense that "deposition" is used elsewhere. They are translocated there somehow.

3-21, 27: Is it true that prolonged clearance in the nose is associated with bronchiectasis? I can see it for the other conditions, but can't rationalize it for that one.

3-23, 7: It is not "deposition" that reaches 1 mg/g lung, it's "retention", or "retained lung burden".

3-27, 35: This section is redundant by repeating information given earlier.
3-28, 2: You might as well be consistent. On page 3-2 line 1, it is stated that the range is 10-40%, not 10-30%. Which do you prefer?

3-33, 26: Insert "size" after "aerosol".

3-34, 3: Here, it is estimated that most of the organics leave the soot in the lung. Earlier, it was stated that soot is "insoluble" due to its clearance being faster than its dissolution.

3-34, 9: With diesel soot a ubiquitous component of ambient particles, how could you state that human exposures are not likely to be continuous. They should be more "continuous" than not.

3- 35, 4: "in humans" should be added at the end of the sentence. It is not always clear which species you are talking about.

3-36, 1-2: The difference could also very likely be due to the difference between inhalation and instillation.

3-36, 12: It should be noted that these results also provide evidence that much of the released organic material passes out of the lung and thus is not available as a carcinogenic dose to the lung.

3-38, 21: It is not clear why, or how, the term "inert dust" is being used here.

3-39, 13: It is not clear what the statement about elution means. Why would elution be faster at bifurcations? Why would it be faster at ambient exposure concentrations?

3-41, 7: End the sentence with "in humans" to keep the issue straight.

Chapter 4: Mutagenicity
General Comments
This chapter is basically in acceptable shape.

Specific Comments
4-5, 5-13: It would seem that the work of Wallace et al. at NIOSH should also be cited. They documented mutagenicity when whole DPM were incubated with cells in a medium containing surfactant components. For example, Keane et al., *Mutation Research* 260(3): 233-238, 1991.

4-7, 11: Move the "the" to after "of".

Chapter 5: Noncancer Effects
General Comments

There is some confusion regarding the citation of some of the work described, but with minor editing, this chapter is satisfactory.

Specific Comments

5-7, 15: Do you mean nasal lavage, lung lavage, or both? I don't know what a "nasal lung" lavage might be.

5-9, 6: With very few exceptions, DPM is not a "major" component of SPM. This statement conflicts with data given elsewhere in the document.

5-9, 11: What is a "filtered solution of DPM"? Do you mean the filtrate that resulted from filtering a solution of DPM? It would also be important to note the medium used for the solution (ie, saline? Solvent?).

5-24, 33: Start a new paragraph with the "White" sentence.

5-34, 25: It is important to note that these were Chinese hamsters, not Syrian hamsters as most would presume if not told otherwise.

5-37, Table 5-6: You should be consistent in listing all of the references for a given study that are cited in the text. This is done inconsistently. For example, shouldn't the Wallace et al. citation be listed for the Barnhart et al. guinea pig study? If not, then a separate Wallace study is missing from the table.

5-40, 32-33: Is there any evidence that speed of onset of an effect is related to the life span of the subject? Why would one imagine that it was? Certainly, one would expect a greater evolution of effects if a longer life span allowed the exposures to continue, but that doesn't mean that failure to induce an effect at an equivalent lung burden might be explained by life span. This speculation might possibly be true, but one would have to bet against it without some evidence.

5-41, 11: The paragraph should be started with the reference, or readers will naturally assume that you are still talking about the HERP study.

5-42, 25: Why list the starting age when you don't for any of the other studies? Conversely, if it's important, why not list it for all?

5-43, 29: Here and elsewhere, the exposure for the Mauderly and Henderson studies (which were the same study) should be listed as 7.1 mg/m^3 to be consistent with other citations in the document, and with the real concentration of 7.08. It's actually listed both ways in this chapter, and should be consistent.

5-44, 11: Again, is this a separate study, or should it be cited with the Barnhart study in the table?

5-44, 23: Similarly, is the Fedan report part of the Lewis et al. study? If so, cite it in the table. If not, it's missing from the table.

5-46, 20-25: There is something wrong here. First, if there was a two-fold increase in the inflammatory mediator LTB4 in both rats and mice, why do you cite a larger increase in rats as the basis for their greater fibrogenic response? Second, none of the reports cited gave and data for either PGF2a or LTB4, because those measurements weren't performed. You must be citing some other study.

5-50, Table 5-7: The Hatch et al study wasn't an exposure to "diesel exhaust"as the table tile states, it was a study of instilled soot.

5-52, 15-16: The lung burdens also progressed over time at the lowest exposure level. They never got very high at that level, but it's wrong to imply that they didn't increase during the exposure, because they more than doubled from 6 mo to 24 mo.

5-64, 27: The study described did not indicate that the pyrene in DPM had an adjuvant effect. It indicated that both pyrene and DPM had the effect, but gave no results to indicate that it was the pyrene in soot that caused the DPM effect.

5-65, 2: First, what is a "dead" pollen grain? Second, how is a pollen grain "burst"? I can see how they can be crushed, but "burst" suggests that they are some kind of a filled container that is ruptured. That's not my understanding of how pollen grains are constructed, but maybe I'm wrong.

5-67, line 8: Eliminate the spurious "0" from the end of the line.

5-71, 15: Change "statistical differences" to "statistically significant differences". Any difference can be "statistical".

5-85, 7: Add "at some level" at the end of the sentence. This is done elsewhere in the document for clarity, and it should be done here.

5-85, 10-11: Animal studies are also done to elucidate mechanisms, so this should be added.

5-86, 21: This evidence is from rats, ans should be noted as such. If there is evidence from other species, it should be cited.

Chapter 6: RfC

General Comments

There are several places where the language needs to be cleaned up, but perhaps the most significant issue is the potential confusion regarding dosimetry based on the carbon core vs. the whole particle.

The other important issue is the use of allergenicity to justify the use of a species UF in calculating the RfC, when you specifically state that lung histopathology will be the basis. For lung histopathology, and its preceding inflammation, it is acknowledged that rats are as sensitive as humans. This seems like double-talk.

Specific Comments

6-2, 6 and 34: If the author does not intend some distinction, the "RfC/D" and "RfD/C" ought to be made consistent.

6-2, 29: "Database factor" ought to be defined the first time it is used.

6-2, 31: Pharmacokinetic and pharmacodynamic are defined on the next page, but they ought to be defined the first time they are used.

6-3, 10-11: The meaning of the phrase "adjustments to the externally applied factors" is not made clear.

6-4, 10: The issue of "known precursor" is a loaded one, and it is not clear what the Agency intends. For example NFKb is typically the first, or one of the first cellular signals one sees when any stress is applied to a cell, but it is a nonspecific "precursor" for a large number of diverse cellular responses, good and bad. If we take the statement literally, then we could use that response as a "critical effect", which wouldn't make sense. As we learn more about biology, we find it increasingly difficult to draw a line as to where a "precursor" response is adverse.

6-7, 10-12: I agree that, as stated, the "whole particle" should be used as the measure of dose, but it is not clear that this is being done consistently throughout the document. No problem here, but there is elsewhere. In line 12, this is chapter 6. What chapter(s) do you really mean in regard to greater detail?

6-10, 8: Here, it is stated that "pulmonary histopathology" would be the best choice for a critical effect, and that allergenic effects might be useful pending additional information. Yet later, allergenicity is used in calculating the RfC.

6-10, 15: Here and subsequently, of what possible importance is the "target" concentration? Why not use 7.1 mg/m^3 for consistency with other parts of the document?

6-13, 15: Here you talk about the carbon core. Earlier, you stated that the whole particle was to be the measure of exposure.

6-13, 19-20: The issue of "final lung burden" is not clear. Do you mean that you want to calculate the exposure concentration of soot that would yield a human retained lung burden at 70 yrs of age identical to that of a rat at 24 months of exposure? If that is so, just state it that way instead of referring to a

"final" lung burden. Are you considering the 70-year exposure to all occur in adults, rather than starting with immature animals as in the rat studies? The description could be made a bit clearer.

6-13, 25: Here, does "DPM" mean the whole particle, or just the carbon core. Here is where the ambiguity in wording really comes back to haunt you.

6-20, 5: Do you mean the lower 95% confidence limit? If so, state that.

6-22, 1-2: Why do you invoke allergenicity here, when you explicitly stated that you are using the lung histopathology for determination of the RfC? It makes a big difference, because the document acknowledges that rats are equally or more sensitive than humans to lung inflammation. That would indicate that no UF is needed to go between species. Invoking allergenicity as your justification seems illogical, and could even appear underhanded.

6-22, 27: It is true that diesel soot is capable of penetrating to the lung, but the statement doesn't make sense. The pulmonary (if that's what you mean by "lung") deposition fraction for 2.5 µm particles is actually higher than that for 0.25 µm particles. The fraction for smaller particles doesn't increase until below about 100 nm. Justifying a greater concern for diesel soot than for $PM_{2.5}$ on the basis of "penetration to the lung" doesn't hold water, and is unnecessary. There are plenty of reasons to be concerned about diesel soot, but that isn't one of them.

Chapter 7: Carcinogenicity
General Comments

Overall, this chapter is in reasonable shape.

Specific Comments
7-81, Section 7.2.6.6: This section relies heavily on the "Bradford Hill" criteria, yet does not cite the source. While "epidemiologists and biologists" have often used the criteria described, it is not very accurate to say that they provided them. The seminal reference to which we all refer is the following, and it should be properly attributed and cited in the reference list:

Hill, A.B., The Environment and Disease: Association or Causation? *Proc. Royal Soc. Med.* 58: 295-300, 1965.

7-126, 21: "In animals" should be inserted after "exhaust".

7-140, 6-10: This sentence doesn't seem to make sense. It is true that inflammatory and/or overload responses are not seen at ambient concentrations. It is also true, in my view, that the animal data are not completely irrelevant for hazard assessment. However, one does not follow from the other; ie, it is

not because responses are not seen at low levels that animals are not irrelevant. These are two different ideas, and the wording needs to be changed.

Chapter 8: Cancer Dose-Response

General Comments

It is important that you state more clearly just what work is underway or planned that is likely to place the Agency in a stronger position to conduct a dose-response assessment in 2000. This is mentioned multiple times in the document, and is a very important and contentious issue, but nowhere is the work actually described.

Here, we have for the first time the "highly likely" business. See the comment on this at the beginning of this review. I don't agree that the term "highly" should be used, and especially not to refer to environmental exposures.

Specific Comments

8-5, 36: Insert "in rats" after "conditions", to make it clear just what you are referring to.

8-7, 2 (and associated citation in reference list): It is Mauderly et al. 1987, not 1997.

8-8, 4-12: It would be appropriate to cite the recent Valberg meta-analysis of the rat data here. That was a mathematical evaluation of the low dose dose-response and threshold issue, and it would be a gap to fail to cite it. The reference does not mitigate against the Agency's bottom line, in fact, it supports it.

8-12, 1-4: This document mentions in several places the new work going on that might result in a clearer picture in 2000. Nowhere is that work described. The reader is left to his imagination regarding this mystery. Here or somewhere, the new, or ongoing effort should be at least briefly outlined. The statements aren't very credible without that. This is especially important because it is such a large factor in the approach the Agency has decided to take in this document, and is also a very controversial issue. There is no reason not to be more explicit.

8-12, 11: I doubt that the "undercount" is being funded, as stated. Rather I think that an attempt to remedy the undercount is being funded.

8-13, 15: Change "give" to "given".

8-16, 9-10: First, the wording of this sentence needs to be changed. It presently states that the "uncertainty – should not be confused with the inference". I think I know what you mean, but you don't state it correctly. Second, I do not agree that "highly" should be used here.

Chapter 9: Characterization of Health Hazard

General Comments

One big issue in this chapter is the use of the allergenicity response to justify the PD UF, when you explicitly stated that the RfC is to be based on lung histopathology and that the confidence in the allergenicity response is not yet to the point where you can use it. This is an important issue.

The second big issue is the use of the description "highly likely".

Specific Comments

9-1, 31-32: I believe that this is the first time the acute responses have been referred to as "temporarily debilitating". If that term is used in Chapter 5 as a conclusion from the literature, I stand corrected. If not, it doesn't seem appropriate to introduce that terminology here, and especially without explanation or definition.

9-2, 3: Insert "other" after "with". Diesel soot is ambient fine particulate matter.

9-4, 21-24: Where is it substantiated that these are the key toxicological components? Is this for all toxicological effects, or only cancer?

9-6, 19: Is "TEQ" defined?

9-10, 4-7: Here again, we have the introduction of allergenicity to defend the PD uncertainty factor. That flies in the face of your having selected lung histopathology as the basis for the RfC, and won't pass muster without better explanation and defense. If you do this, then you must state that you are using both lung histopathology and allergenicity as the basis for the RfC. You stated very clearly earlier in the document that you didn't consider the evidence for allergenicity to have matured to the point that it could be used for this purpose.

9-10, 15-17: The meaning of this first sentence is not clear. It states that the output of an RfC assessment is not a science-based process, and I doubt that's what you mean.

9-10, 20: "Can be" should be changed to "are". There are very few samples in which diesel soot is not a component of ambient $PM_{2.5}$. I'd challenge you to find one.

9-15,. 12: I do not agree with the use of "highly" as pertains to environmental lung cancer risk. I have no problem with "likely".

9-16, 7: Change "ventilatory frequency" to "minute volume". It isn't the breathing frequency that's important here, it's the greater ventilation of children than adults per unit of lung surface.

John Elston

In general, my impression of the Health Assessment Document for Diesel Emissions is favorable as compared to the earlier draft reviewed by CASAC last year. EPA's conclusion that a "bright line" reference concentration is appropriate for non-cancer health effects while a "bright line" unit risk factor is not yet appropriate for cancer effects seems supportable given our current knowledge. While I did not support a subsequent CASAC re-review of this document I do believe such a review is appropriate if it can be conducted in a timely matter and limited to only the revisions suggested by the panel. If indeed, diesel emissions "likely" show an association with cancer this information must be made available to the Administrator as quickly as possible. In the absence of EPA's inability to enforce the PM2.5 NAAQS because of the recent Appeals Court decision, it is vital for CASAC to reach closure on this document so that EPA can act accordingly.

My specific comments will pertain primarily to Chapter 2. While this chapter has been completely rewritten and vastly improved its content now allows a number of new questions and comments to be offered.

For one, it is important to accurately portray the past, present, and projected future diesel emission inventory. The past inventory is needed as a time sequence to correlate with earlier epidemiology studies and the present is needed to ascertain verification of recently manufactured diesel engines meeting the current standards. In-use diesel emission studies and data are extremely weak, yet EPA has assumed a six (6) fold improvement over time. Given the EPA experiences with the diesel manufacturers use of apparent "defeat" devices for controlling NOx emissions, how can we assume an in-use improvement which would mirror the changes in the regulatory standard? The simple answer is we can't. Given the many assumptions of in-use diesel verification (i.e., deterioration caused by wear and variations in diesel fuel, gross vehicle overloading, operator driving discretion and others) it is unlikely that the real world diesel emissions will match regulatory standards. A realistic real world model is required to predict present and future diesel emissions.

EPA also tends to downplay the recent revelation that ultra-fine particles are an important public health consideration of diesel emissions. Ultra fine particle characterization is vital for determining particle number and composition. EPA has assumed a more or less proportional relationship of PM10 and PM2.5 concentration and composition. This may not be true for ultra fine particles. Characterization of ultra-fine particles under various engine operations, including cold start-up and cool down idling conditions are also needed to represent population exposure adequately. Moreover, the biologically active components are also assumed to be proportional. A case has not been made for this assumption.

Finally, it seems to me, that the exposure analysis in Chapter 2 is relatively weak. Maximum exposure situations and locations, even in lieu of a study, should at least be hypothesized. For example, residents living along and at the end of bus routes, locations of prolonged diesel truck idling, residential locations where diesel locomotives idle overnight. Community situations such as these can be relatively common

in some areas and diesel idle emissions (assuming cool down engine conditions particularly in winter) may have a different composition due to the combustion of lubricants under these conditions.

These comments should be considered for future studies. Otherwise, I believe the Chapter is well written and the basis for the conclusions are relatively clear and sound.

P.K. Hopke

Chapter 2

The critical outcome of the chapter needs to be that the basic nature of the emissions from diesels has not changed and thus, the historic toxicological effects that have been related to diesel emissions are still valid. There is not a convincing argument in the chapter. They have done a very good job of updating the chapter, but there is a strong indication that the organics associated with diesel emissions have decreased. This provides prima fascia evidence that the nature of the emissions have changed and thus, the toxicological properties associated with that OC phase have been reduced per unit mass of PM. Thus, more attention needs to be made to close this argument or else specifically state the assumption that the diesel particles are as toxic on a per mass basis since there is no other evidence to go on and that provides a protective upper bound estimate. However, this issue needs to be dealt with more clearly and forthrightly.

1. Page 2-15, line 1: do you mean relative to 4-stroke designs?
2. Page 2-35, lines 15 and 16: is there really an extra digit available for off-road (0.0322) or is there a trailing 0 missing from on-road (0.0320%)?
3. Should include NFRAQS data into report. They must have measured criteria pollutants as well as speciated organics.
4. Page 2-44, line 35: soluble in what? Need to say what the solvent is.
5. On 2-46 the solvents are given for Rogge et al. (line 32), but not for lines 23, 25, 27, and 28. Are these all the same solvent or is the polarity defined by the solvent? If so, it needs to be given.
6. It would be helpful to tabulate all of the engine testing studies even if they are not explicitly described in the text on page 2-47.
7. Page 2-61, line 2: more than “several” compounds are emitted as gaseous exhaust components. Delete “several”.
8. Page 2-74, line 23: What does the NRC report have to do with gasoline powered vehicles in Denver? It is not clear how represent the selected vehicles were nor the effects of altitude and fuel formulation. Thus, the NFRAQS findings are interesting, but should not be over emphasized until they can be shown to really be replicated in other locations. However, the references should be to NFRAQS reports and not to the NRC report.
   It is premature to utilize these ratios as done on lines 30-34 and that material should be deleted.

9. Should be an indication of the potential for other receptor modeling approaches are possible given speciated hydrocarbon data. For example, there is Henry et al. (*Environ. Sci. Technol.* 28:823-832, 1994).
10. Page 2-76, line 8: NRC is not the correct reference.
11. Page 2-76, line 24: what year were the measurements made? Since diesel emissions have been changing, it is important to provide dates for all measurement campaigns.
12. Page 2-77, line 34: Claremont is not a county. It is a location near the border of Los Angeles and San Bernardino Counties.
13. What about the bus stop exposure scenario? We see the clouds of black smoke coming from many urban buses that have to result in short term extreme concentration values. Are these considered? Should they be?
14. There is no discussion of military vehicle contributions to ambient diesel concentrations. Military vehicles are either diesel or gas turbine and in many areas would represent significant off-base sources.
15. Unlike many other types of particles, studies of diesel particles have suggested that there is no hygroscopic growth. This information should be provided. Appropriate references are Dua, S.K., P.K. Hopke, and T. Raunemaa, *Water, Air, and Soil Pollution* 112:247-257 (1999) and Weingartner, E., H. Burtscher, and U. Baltensperger, *Atmospheric Environ.* 31:2311-2327 (1997).
16. In 3.3.3.3, you list a number of issues including age, gender, physical activity, respiratory tract disease, and irritant inhalation, but only respiratory tract disease is discussed (3.3.3.4). Why aren't the other issues worthy of discussion if they are worth listing?
17. Page 8-1, line 9: "shows" seems an overstatement "suggests" seems more appropriate.
18. Page 8-2, lines 6 and 7: ratio should be diesel/coke oven. Then when multiplied by coke oven potency would estimate diesel potency.
19. Page 8-7, line 24: ". . . what is happening in the human lung is uncertain" is in conflict with "shows" that it is a "likely" human carcinogen.
20. Page 8-11, line 14: in general epi never gets rid of confounding factors. To some extent it can control for them but there are inherent collinearities. Thus, to single out this problem for diesel undermines epi for all quantitative risk assessment.
21. If we can expect more results from Steenland next year, what will it take and when will we have a quantitative risk assessment? What do you do vis-a-vis regulation in the interim? Can't an adequate upper bound be estimated?
22 On page 9-6, line 16 it is the Desert Research Institute.
23. Page 1-1, line 14 needs to say mass median diameter since the number median diameter is more like 70 to 80 nm. The number distribution is more important since it better describes the distribution of particles sizes as they pertain to deposition and it would be better to switch to number distributions throughout the document.
24. Page 1-1, line 23, any combustion source produces EC particles. It is only a matter of proportion. Remove "almost unique." Diesel is a major source of EC but by no means the only source particularly in areas with oil-fired home heating.

Art Upton

I regret that I'll not be able to attend the Dec. 1 CASAC meeting, but I have reviewed the assigned chapters in the revised Health Assessment Document for Diesel Emissions, and I consider them to be acceptable in their present form. I have no substantive changes to suggest.

Sverre Vedal

Chapter 1 Executive summary
Minor comments:
1-1 I would add a quantitative estimate of the contribution to DE to PM2.5 here (line 22).
1-2 Define RfC here (line 16), since only defined later on this page.

Chapter 7 Carcinogenicity
This chapter is improved over the previous draft. The review is thorough and appropriately critical. The conclusion that diesel exhaust is highly likely to be a human carcinogen and at environmental concentrations is well supported and appropriately conservative.

The application of the Hill criteria for causation is not done well and is not very informative. Regarding temporality, it is difficult to imagine a scenario where this criterion would not be met given the designs of the studies. Regarding strength of association (7-82), nowhere is strength addressed. This should refer to the size of the effect estimate rather that to consistency across study as was done. When one does consider strength, it is clear that this is at least one criterion that is not met (e.g., rate ratios of around 1.3-1.5). The claim that all criteria have been met (7-85, line 21) is not true. Regarding specificity (7-83), this is addressed by determining whether the association is specific to lung cancer, compared to other types of malignancies. Obviously only cohort studies can address specificity within any given study, and this has seldom been done. In short, consideration should be given to dropping the Hill criteria discussion unless it is felt that the above issues can be addressed well. My preference would be to drop it..

Latency is an important issue that needs to be discussed further. One could argue that all of the studies, not just those excluded, suffer to some extent from having relatively short latency periods (period from onset of significant exposure to time of disease ascertainment). By my reckoning, this is around 20 years. The Garshick analysis currently in progress should address this concern. If I am off base on this issue, then arguments showing that latency periods were in fact longer than that, or that such relatively short latency periods are realistic, should be made.

As I noted at the last review of this document, I do not understand the exclusion of "hypothesis-generating" studies (7-2). First, many studies included (the case-control studies in particular) could be described in that way, given the interest in many exposures. Second, at this point in time there is no logical primacy to hypothesis-driven as opposed to hypothesis-generating studies. There may be other

reasons for excluding some of these studies (e.g., the Schenker study was a pilot study of the later Garshick study), but the argument regarding hypothesis-generation does not seem relevant.

Lastly, the issue as to whether cigarette smoking is confounding the association has been reasonably well addressed in the current draft. I recall that a significant amount of sensitivity analysis was performed on the Garshick cohort study regarding the effects of a range of cigarette smoking scenarios, and that the results of these sensitivity analyses were reasssuring. I did not see these data in the current draft (unless I overlooked it) and feel that they are important data. The issue confounding by smoking has not completely been put to rest given the relatively crude approaches taken in the relevant studies for controlling for cigarette smoking. Perhaps the most reassuring observation is that although smoking is a strong predictor of lung cancer, it is seldom, if at all, associated with exposure.

Minor points: 7-27 small *cell* ca (line 35).
7-36 lung *carcinogens*, not lung *cancer* (line 19).
7-39 (line 32) what does "risk...higher than the OSHA standards" mean?
7-40 (line 9) no ref. to HEI,1999.
7-74 (line 30) clarify that age was at time of enrollment (1959).
7-140 (line 24) "inferences" are *always* involved, so the point is not clear.
7-143 inadequate referencing of lung ca and air pollution (modern cohort studies of Dockery, Pope, and Abbey, and recent review by Cohen and Samet, etc.).

Chapter 8 Dose-response
This chapter is well done. My criticisms are minor:

8-10 Beginning at line 35 and continuing to the first 3 sentences on the next page contain some incomplete and meaningless sentences. I wonder whether some parts of sentences were inadvertently deleted.
8-12 *covariate*, not *covariant*, in line 20.
8-14 I cannot follow the reasoning regarding the link between effect estimates and lifetime risks of lung cancer.

Chapter 9 Health hazard and dose-response
Only editorial:
9-3 *or* should be *for*

Warren H. White

CHAPTER 2: Diesel emissions characterization, atmospheric transformation, and exposures

This chapter is a tremendous addition to the HAD. For something that is essentially a first draft as this chapter is, it is impressively comprehensive and balanced. It was very helpful to my understanding of

the diesel issue. If the Agency is to approach DE as a distinct and identifiable "pollutant", it is essential that it address the historical and prospective homogeneity of DE as it does here.

2-6/11: There appear to be words dropped between the end of page 2-6 and the start of page 2-7.

2-7/9: The 1998 trends report presumably takes us up through 1997 rather than 1977.
2-7/13: more to the point, "Mobile sources include both gasoline- and diesel-powered on-road vehicles and a variety of off-road equipment."
2-7/16: more clearly, "The EPA emission trends report shows that, excluding fugitive dust sources, mobile sources are responsible for 24% of PM10 emissions, with stationary point and area sources responsible for the remainder."
2-7/20: The basis of this comparison ("much greater") needs clarifying: is it per-vehicle, per-horsepower, national aggregate? Bear in mind that NFRAQS estimated that gasoline vehicles contributed more than diesels to ambient PM2.5 in Denver in the winter.

2-8/5+: The percentage figures are unhelpful, because the reader has to do the math anyway to know whether 53% is 56,000/120,000 or (120,000-56,000)/120,000. I suggest "decreased 53% (from 120,000 to 56,000 tons)"
2-8/13: "direct emissionS" – plural to agree with verb "are"
2-8/28: "engine-out" is jargon that requires introduction

2-9/18: The opening sentence of this paragraph should be the closing sentence of the preceding paragraph.

2-13/2: for clarity, replace "this" with "assessment of their impact"
2-13/3: "a different extent" should be "differing extents"

2-15/1: "2-stroke" should be "4-stroke"

2-17/29: "There is little evidence to suggest .." needs to be reconciled with "the Ames assay indicated .." in lines 25-26.

2-24/11: "the prevalence of" is redundant with "penetration"

2-30/13: "In the years since 1950 to 1990 and beyond" is meaningless!
2-30/16-19: I don't believe that the ratio (combination truck vehicle miles)/(passenger car vehicle miles) in 1997 was (124,500 billion)/(1,500 billion) = 83.

2-36/6: What is "GVWR"? 8,500 lbs isn't very heavy for a truck!

2-46/8+: I would like to see more discussion of the extraction procedures and their influence on measured SOF.

2-47/20+: This discussion of DEP minus SOF, the non-extractable residuum, is important and deserves at the very least a new paragraph of its own. In chapters 1 and 9, the equation DEP-SOF = EC is taken for granted. Besides the Zielinska NFRAQS data, the Rogge et al. (1993) paper cited at 2-46/32 also measured EC.

2-56/28: "the general" should be "a generic"

2-60/9: "with no sampling artifacts" should read "in the tailpipe". "Artifacts" are relative to a measurement's interpretation and use.
2-60/18: The remark that > 90% of DEP is likely generated during transients merits emphasis in Chapters 1 and 9 as a factor limiting our present knowledge of real-world emissions.

2-74/16: According to 2-47/20+ (see comment above), this discussion addresses DEP-SOF, the portion of DEP left by unspecified extraction procedures, and not actually EC. How about "soot" as an alternative term?
2-74/26: The intended reference is NFRAQS, 1998, which the National Research Council had nothing to do with. This citation error extends even to the bibliography.
2-74/27: Note that these values contradict the Executive Summary's claim (1-1/23) that "the elemental carbon core is nearly unique to DE".
2-74/31: Where does the figure 64% come from?

2-77/6: The similarity of indoor and outdoor PM2.5 levels might suggest "extensive intrusion of outdoor air into the school environment", or it might instead suggest only the presence of indoor sources such as chalk dust and the activity of children.

CHAPTER 9: Characterization of health hazard and dose-response for diesel engine exhaust

Overall, I liked this chapter. It is generally readable and succinct, written in plain english, and very helpful in putting issues in context. The exceptions I found to this pattern are listed below.

9-1/31: should read "ranging from annoying TO temporarily debilitating"

9-2/9: This chapter is addressed to a more general audience than some of the earlier chapters. For much of this audience, "Mode-of-action information provides a framework" is opaque jargon.
9-2/35: Schauer et al. (1996) did not address "nationwide" diesel contributions.

9-3/10: should read "characteristic OF"

9-3/13: more accurately, "The main constituent by weight of the diesel particle is NON-EXTRACTABLE CARBONACEOUS MATERIAL, OFTEN REFERRED TO AS elemental carbon"
9-3/15: more accurately, "with 80% being typical IN RECENT MEASUREMENTS"

9-4/12: There is no section 2.2.7.
9-4/12+: This paragraph gives the impression of straining to make the case for "mg/m^3 .. as the dosimeter" (see also next comment). A more balanced discussion might note the declining organic fraction (cf. page 2-47):

> "Chassis dynamometer results indicate that SOF emissions have trended downward over the years as engine manufacturers have tried to reduce oil consumption. This is shown in Figure 2-19, where the trend can be seen as .. reduction in SOF weight percent... The downward trend in SOF as a percentage indicates that the solid carbonaceous material as a percentage of PM has been increasing. ... Engine testing studies show SOF percentage to be highly variable, .. exhibiting a declining trend with model year [eight citations]."

A more balanced discussion might also note that (page 2-32) "Most important for emissions, the chemical makeup of diesel fuel has changed over time, in part because of new regulations", and that (page 2-17) "the Ames assay indicated that the SOF produced by EGR was more mutagnic."
9-4/28: The phrase "mg/m^3 is used as the dosimeter" is jargon. It should be replaced, here and subsequently, by "mass concentration ($mg/m^{3)}$ of DE particles is used as the dose metric".

9-5/33+: This paragraph is self-contradictory. Do CMB estimates of on-road and off-road DEP at fixed sites in urban and suburban areas range from 4.4 to 11.6 mg/m^3, or from 1.2 to 3.6 mg/m^3?

9-7/31: The sentence "While the applicability of rat .." is hard to parse. I think the authors mean "The relevance to humans of rat lung cancer responses has been questioned. The relevance of noncancer responses in rodents is more generally accepted, although the rat is more sensitive ..."

9-8/9: How does observing rodents <u>demonstrate</u> that "(4) <u>it is believed that</u> the adverse effects have a biological threshold, there being no available evidence to the contrary"? And is there any unambiguous evidence <u>in support</u> of a threshold?
9-8/22: more clearly, "The majority of DE particle mass is at the fine end of the respirable range"
9-8/26: more clearly, "Inhalation Reference Concentration (RfC)" [i.e., need to introduce abbreviation RfC for subsequent use]
9-8/30: If the authors are going to talk about "dose/exposure rates of DE", then for consistency they should talk about the concentration of "DE particles" or "DEP" rather than the visually unrelated "diesel PM".
9-8/33: more clearly, "A reliable database FROM ANIMAL EXPERIMENTS and established EPA .."

9-9/7: need to introduce NOAEL.
9-9/9: This "critical" is not the "critical" defined just two lines earlier; an alternative like "key" might be less confusing.
9-9/17: more clearly, "The process of RfC determination benefits from this unusually large number .."

9-11/1: Why do we need a (solitary) subsection and subheading here?
9-11/4: I don't get "This hazard is viewed as being applicable to ambient .. exposures." How does one "apply" a hazard? Do the authors mean that the 1996 determination of hazard is relevant to an assessment of ambient exposures? Who's "view" is this – the 1996 Guidelines' or the present Assessment's? I raise these seemingly minor points because this phrasing recurs throughout the Assessment (e.g. 1-2/32, 7-139/17), suggesting that it conveys some important nuance that I am missing.
9-11/21: Section 7.5.1, which is cited here as supporting the assertion that "causality considerations for this observed association are very consistent" [emphasis added], is actually nothing more than an abridgment of the present section (9.5.1), and in fact omits the "very" from its claim of consistency.
9-11/24: It seems a bit misleading to note that some individual studies had higher risks without also noting that some had lower risks. After all, meta-analyses are essentially sophisticated averaging procedures aimed at narrowing confidence intervals, and it's no surprise to find them yielding combined estimates that lie within the range of individual estimates.

9-12/7-11: The argument here seems tendentious. The fact that job codes and the like are surrogates for diesel exposure means that we expect some systematic association between them and that particular dimension of air quality. Why should we, at the same time, expect them to be completely unrelated to other dimensions of air quality, and to other potentially confounding variables?

9-14/31: But can organics really be "thought to be in relative proportion to the mass of particulates"? – see above comments on 9-4/12+. To do so is to ignore diesel oxidation catalysts, for example, which section 2.2.3.5.2 notes are being retrofitted with EPA support into older urban busses. Also, even my simple-minded word-processor knows enough to flag "particulates" as incorrect.

David Diaz-Sanchez

Comments on Chapter 1
Overall the document is a much better representation of the health risks of diesel than the last draft, The chapters are more inclusive with more references cited. However, there are still too many inconsistencies and errors that give the impression that each chapter was written by different authors who did not read the other chapters. For example, on the very first page it states that "the elemental carbon core is nearly unique to DE" (line 23). Not only is this incorrect, it contradicts the assumptions made further on in the document where only 70% of elemental carbon is assumed to come from DE.

Comments on Chapter 2

This is a much expanded and comprehensive and current version of the previous draft.
Page 2-30, line 18 There is an error in the calculations. Are these values correct?

Eric Garshick

Chapter 5 Noncancer Health Effects
Page 5-1, lines 11-12: These lines refer to the noncancer effects of PM. It would be worth summarizing these effects and discuss how diesel could or could not contribute.

Page 5-6, bottom of page: Three cases of asthma attributable to diesel exposure are described under the heading "Immunologic Effects". It should be emphasized here that these cases were not caused by an immunologic mechanism, but occurred after a short-term exposure to high levels of exhaust. The paragraph summarizing non-cancer effects possible due to diesel exposure (page 5-10) is misleading because it is implied that cross-shift changes in pulmonary function and these cases of asthma after exposure have an immunologic basis.

Page 5-12, line 21: In the description of the paper by Reger et al. (1982) it would be clearer to specify that the number of workers studied included 550 miners working underground and 273 surface miners.

Page 5-67, last paragraph, first three lines: These lines suggest that diesel particle retention in the lungs of humans will cause pulmonary hypertension and cor pulmonale secondary to either pulmonary fibrosis or emphysema. This is not correct, and this assertion appears in the section describing the health effects noted in animals exposed to particles at levels greater than in humans under conditions of particle overload. These lines are misleading because it suggested that diesel exposure is known to cause pulmonary fibrosis, emphysema, and cor pulmonale in humans.

5-96: I disagree with the statement that inflammation and fibrosis noted at high levels of exposure in animals in the setting of particle overload are relevant in assessing human risk at lower levels.

Chapter 7 Carcinogenicity of Diesel Exhaust
General Comments - Epidemiology

The presentation of the various studies has not improved since the last version of the document. In my last set of comments, I pointed out inaccuracies in the descriptions of many studies. These inaccuracies have not been corrected.

The general description of each epidemiologic study often repeats details that are not relevant instead of presenting each study in a form that is easily understandable and coherent. The critiques after each description are repetitive, and do not provide the reader with an understanding of the significance of each limitation that is noted.

Studies of similar design will have the same limitations: use of death certificates, lack of retrospective smoking histories, use of job title as a surrogate of exposure, use of next-of-kin smoking information, and lack of sufficient latency for the development of lung cancer. It is important to summarize these limitations in a concise fashion and point out which limitations are serious and which limitations are minor. There is an effort to do this on page 7-79 and the following pages, but the discussion is poorly organized.

For example, the statement is made on page 7-80, lines 13-15 that reads "Study endpoints are frequently mortality data taken from death certificate information, which is frequently inaccurate and often does not fully characterize lung cancer incidence in the population in question". On the previous page, 7-79, lines 13-19 cites evidence validating the use of death certificates, and stating that if there is any bias at all, it is towards an over-diagnosis which would make it harder to detect an effect of exposure.

The epidemiologic studies have 2 major limitations that are not emphasized. The first is the lack of a study with a large population with many years (consistently over 20 to 30 years) of exposure and follow-up. The second limitation is the lack of exposure information. With the exception of 3 studies, data definitely linking job title to exposure are not available, and the extent of exposure in the past is not available. On page 7-80, lines 12-13 it was written: "Generally, the only information from which diesel exposure can be inferred is occupational data, which is a poor surrogate for the true underlying exposure distribution". However, the issue in not only quantitative as implied by the statement, but qualitative. In many studies, it was not known how well job definition reflected exposure to diesel (i.e., as a professional driver).

Specific Comments:

Introduction: Page 7-1, Comments on PM, lines 19-22: It is not clear to me what conclusions should be drawn from these statements as they are written here. Presumably, it is to bring up the link to PM10 in a chapter that discusses lung cancer, but the significance of this is left up to the reader. What point is the Agency trying to make? My interpretation is that diesel contributes to the general environmental particle load, and that the study of occupational cohorts exposed to diesel exhaust represent subjects with exposure to particles, some of which comes from diesel, but some from other sources, depending on the job. This may or may not be relevant for cancer risk. However, the Six Cities Study suggests that PM may be linked to lung cancer risk.

Page 7-1, lines 23-31: The issue of duration of exposure and latency needed for the development of lung cancer is introduced in a general way. As I noted in my last comments, the change from steam to diesel locomotives generally started after World War II such that by 1946, 10% of the locomotives in service were diesel, by 1952 55% were diesel, and by 1959, 95% of the railroads were diesel. By stating that the transition to diesel started in 1935 implies that most of the railroad workers were exposed for many more years than actually occurred. Since many epidemiologic studies were done in

truck drivers, it would also be useful to state that the trucking industry changed to diesel trucks by the 1960's, and sales in the 1960's of Class 8 trucks (long haul trucks) rose from 48% in 1960 to 85% by 1970. Therefore, in studies of truck drivers that reflected exposures in the 1970's and 1960's, many drivers would have been driving gasoline-powered vehicles.

Page 7-13, study of Garshick et al. (1988): We now appreciate that the relationship (slope) between years of exposure, when adjusting for attained age (rather than age at entry into the cohort) and calendar year, is negative. In the years 1977-1980 we now recognize that death ascertainment was not complete with 20% to 70% missing deaths depending on the year. The use of years of exposure starting in 1959 also excludes exposure before 1959. Before 1959 there could have been up to 10 years or more of additional exposure by some members of the cohort at a time when the intensity of exposure was likely to highest. When analysis of this cohort based on job title in 1959 is limited to deaths occurring through 1976, the youngest workers still had the greatest risk of dying of lung cancer. The description of this study needs updating.

Page 7-36, study of Steenland et al. (1990): It would be appropriate to discuss this study together with the industrial hygiene of Zaebst et al., 1991. This study indicated that the mechanics had the highest level of exposure, and the short haul and long haul drivers had similar exposure levels (approximately 25 $\mu g/m^3$). It is noted on page 7-37, lines 21-23 that no job category had elevated risk. However, the study has been interpreted as being generally positive because of the elevated point estimates. The odds ratio for the mechanics was 1.69 (95% CI=0.92-3.09), 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. These results can be added to the section, and serve to link the air pollution and diesel literature.

Page 7-38, study of Steenland et al. (1998): This is not an independent study, but is based on the case-control study published in 1990. Numerous assumptions were used to generate the dose-response relationships presented. As a result of the uncertain link between job title and level of past exposure presented here, the risk presented is uncertain. The limitations should be pointed out. The statement on page 7-40 "As far as qualitative risk assessment is concerned, this study is considered still to be positive and strong" is not relevant since the original 1990 study has been presented.

Page 7-48, Summaries of studies and meta-analyses: This section provides no new information and it is not clear why it is included. On page 7-50 a comment is made about adjustment for smoking in the 1987 case-control study published by Garshick and coworkers. Pack-years both as a categorical and continuous variable were used in the analysis, not just pack-years as a categorical variable as suggested by the Agency.

Page 7-79: It might be useful to state what is lacking in the human epidemiologic literature regarding the relationship between human exposure to diesel and lung cancer. What would be required to permit EPA to declare diesel exhaust a definite human lung carcinogen? This would help guide recommendations for future research.

Chapter 8 Cancer Dose-Response Evaluation

Page 8-3, Table 8-1: If these estimates have limitations, then it is misleading to list them

Page 8-11, lines 16-17, comments on the effect of cigarette smoking: An analysis performed by in the HEI 1995 report demonstrated that small differences in smoking behavior are not likely to account for the elevated risk attributed to exposure. It would be reasonable to include this in the discussion about the potential effects of smoking.

Page 8-14: This section discusses the magnitude of potential risk of lung cancer. This discussion seems irrelevant given the uncertainty of actual exposure information.

Chapter 9 Health Hazard Characterization

Page 9-11: The designation "likely" seems more appropriate, which is consistent with the prior categorization of the health hazard.

To understand the risk of lung cancer due to diesel exposure, a study is needed that clarifies the relationship between job title and risk of lung cancer. For example, can exposure to diesel exhaust alone account for the risk of lung cancer attributed to working as a truck driver? Is it due to properties unique to diesel, or is it due to an ill-defined effect of respirable particles? It would be reasonable to pose such questions in this section.

Comments on Chapter 5

This chapter is an obvious improvement over the previous draft. The range, scope and number of articles on non-cancer effects of diesel exhaust has been considerably extended and updated. The omissions are mainly extensions or confirmation of work already cited in the chapter (e.g. Muranaka 86, Suzuki 93, Ichinose 97, Terada 97). One area where studies are oft omitted do bear mentioning: the role of diesel exhaust and components of the organic fraction on immunological changes *in vitro*. For example: Saneyoshi 97 and Fujimaki 94 which deal with cytokine production from cells derived from diesel exhaust treated animals. However, overall I do not believe that the omissions seriously detract from the quality of the chapter.

Epidemiological studies have been of limited value to determine the non-cancer health effects of diesel exhaust. As the chapter points out they have been plagued by many of the same confounders as the

cancer studies: quantifying of exposure, the effects of smoking etc. Additionally, pollutants such as ozone and environmental tobacco smoke (ETS, second hand smoke) are thought to be risk factors for respiratory diseases, asthma and atopy, thereby further complicating the picture. Several studies that have not been cited examine the role of environmental pollution in the incidence and severity of respiratory disease, asthma, atopy and other immunological diseases. However, these studies are plagued by the inability to dissect out one element such as diesel amongst the general mixture. Given these limitations I believe that the document is correct in drawing few conclusions from these studies. In contrast the experimental exposure studies on humans are informative and there can be little doubt that diesel will cause odor, eye and lung irritation. More obviously these studies demonstrate inflammatory and immunological changes. These results are confirmed and strengthened in the various animal models and direct comparisons of the human and animal studies would be useful. Although the separation of studies into human and animal is valid, a better attempt to link the two could be made.

The chapter correctly identifies that the studies cited demonstrate only limited evidence for a detrimental effect of DPM on liver function, microsomal enzymes, serum biochemistry, fertility and bacterial resistance. The data for an effect on pulmonary function is much stronger and the risk of reduced pulmonary function as a consequence of chronic DPM exposure is correctly identified.

It is in the category of inflammatiory and immunological changes that this chapter is most lacking in interpretation. While most of the relevant studies are cited it seems clear that there is not a complete grasp of the significance of the results. Table 5-8 is cited twice as showing “equivocal results”. In fact all the studies shown in this table and in Table 5-9 are in agreement. It is clear that DPM alone increases inflammation while in the presence of allergen it will cause an increase in “allergic antibody” production and the induction of responses typical of asthma. The fact that there is no apparent change in the first 3 studies cited (Dziedzic 1981, Mentnech 1984, Bice 1985) is completely expected and agrees with the other studies. These 3 studies measured total lymphocyte number, IgM, IgG and IgA antibody production. In fact these endpoints would not be expected to increase in an asthmatic or allergic response or even in a general inflammatory response. An increase in neutrophils with possible bronchial hyperplasia would be expected in the absence of allergen alone. With allergen, an increase in eosinophils, mucus and IgE production would be expected. this is exactly what is seen.

Overall it seems obvious that the authors of this chapter were more comfortable with established issues such as airway clearance and alveolar macrophage viability and have stressed these points even though the data for them is contradictory. It should be noted that immunity, allergenicity and inflammation are all intricately linked. Studies in human, animal models and in vitro assays are all virtually uncontested for a role of DPM in inducing immunological changes that promote inflammation and allergic airway disease. Indeed given that of the 50 studies cited in this chapter published after 1990 more than 2/3 refer to asthma/allergy or immunological, it is surprising that this chapter does not lend more emphasis to this point. It seems clear that although whether these effects occur at environmental or occupational concentrations have not been determined, diesel exhaust can alter the immune system to induce or exacerbate inflammatory and immunological responses.

Comments on Chapter 6
Despite the preponderance of evidence showing that diesel exhaust can affect immunological changes, the quantitative data in this area is virtually absent. Therefore, the authors are correct in choosing pulmonary histopathology as the critical effect from which to derive the Rfc as this is the field with the greatest amount of quantitative data. It is stressed throughout the document that the authors believe that this health outcome is due to the carbonaceous effect of Diesel Exhaust. The authors should therefore clearly explain why the derived Rfc is different from that set for PM2.5.

The issue and use of uncertainty factors is very problematic. A value of 10 is used to accommodate human-to-sensitive-human extrapolation. The main justification used for this value is that certain individuals may be more sensitive to the effects of DE on allergenicity than others. How can the authors choose one disease outcome for the critical effect and a completely different one the uncertainty factors? This leap in logic seems even more egregious when one reconsiders the mechanisms of these two outcomes: pulmonary histopathology is considered to be caused predominantly by the carbonaceous core of DEP while there is very compelling evidence that the allergenic changes are due to the chemicals present in DEP.

Given the previous criticisms it is surprising that a "high confidence" is expressed in the Rfc. What does this mean? Is this a merely subjective descriptive label? Are the authors comparing this to other Rfc derivations the agency has made?

Comments on Chapter 7
The designation of the carcinogenic effects of diesel exhaust as "highly likely" seems again subjective and capricious. While it seems the evidence certainly suggests that diesel is a possible carcinogen, the moniker "highly" is redundant and confusing. This category should be clearly explained apropos the EPA's proposed guidelines for Carcinogen Risk Assessment. What is the criteria for classifying DE as "highly likely" rather than "quite likely", "somewhat likely" etc.

William Pierson

I would not agree that it has been demonstrated that diesel PM is a human caracinogen at occupational/ambient levels. Also, the report seems unreasonably long for human absorption.

Ronald E. Wyzga

Chapter 2: Can anything be said about the general public's exposure profile to diesel emissions; i.e., what is the distribution of diesel emissions concentrations and personal exposures over time? Are peak exposures common and much higher than longer term averages?

Chapter 5: The linkage between this chapter and the PM health effects literature is woefully inadequate. In particular, it would be of interest to learn where there are similarities and differences in the findings.

Chapter 6: I have three major comments on this chapter: (1.) The concept of "average lifetime exposure" should be defined unambiguously: I assume that this means a 24-hour a day exposure for lifetime (70 years). (2.) This concept then need be related to typical exposure profiles to the extent that these are available. (I believe a key research need is the development of such profiles.) In any case the realism of the lifetime exposure concept needs to be addressed and confronted. To what extent, for example, is there support for Haber's law with respect to these emissions? Is an RfC/RfD based upon "average lifetime exposure" really useful for non-cancer endpoints? I personally believe that more acute exposures may be far more important for non-cancer endpoints; I would at least have liked to have seen a discussion of this issue. (3.) Finally there are relatively few linkages to the PM Criteria Document and health effects literature. If diesel emissions were associated with health responses as PM in general, the evidence for associations is clearly greater for acute exposures.

Specific comments:

p. 6-6, ll 6-8: This is speculative. More information is needed to buttress this assertion.

l. 29: Does this model apply to ultrafine particles?

p. 6-13, ll 23-27: Insert that this applies to an assumed continuous lifetime exposure.

p. 6-22, l. 7: It should be stated unambiguously that this refers to a continuous lifetime exposure. Does this then translate into the equivalent of an annual standard? If so, compare it with the PM standard? Is there any evidence that such exposures are ever attained?

Chapter 7: I have several general comments about this chapter. (1.) I am uncomfortable with the use of the term "highly" in summarizing the carcinogenicity of diesel exhaust. This adjective is not part of the classification language suggested for use by EPA, and I fear that the use of such adjectives will only confuse the public even though EPA can apply descriptive terms as appropriate. (2.) The meta-analyses discussed in the chapter cite a greater number of references than the EPA document. Is there a good reason for this? (3.) There is no discussion in this chapter of the reanalyses by Crump and Dawson of the Garshick data. We specifically asked EPA to try to resolve this issue in our previous comments on the draft document. This issue was apparently addressed by a group from HEI, alluded to in Chapter 8 (p. 8-12); this should be thoroughly discussed in this chapter. (4.) Again linkages to the PM issue are weak. See, for example, Table 8-7 in the current draft PM Criteria Document. Such linkages could lead to a discussion about the importance of chemistry as opposed to particle exposure per se.

Specific comments:

p. 7-2, ll 1-4: I don't believe that EPA should dismiss "hypothesis-generating" studies as readily as it did. These studies, particularly if they are negative, provide useful information in interpreting the overall information.

p. 7-54, l 9: What is "relatively technical"?

p. 7-71, ll 3-20: Good discussion.

p. 7-82, ll 14-16: Why are only "some of the studies considered by HEI ...considered in this chapter"?

p. 7-138, l 32: This is Chapter 7; give section or page number.

Chapter 8: General Comments: (1.) I applaud the EPA's willingness not to estimate dose-response relationship from the extant data. This is in contrast to the usual practice, but it is warranted by the data currently available on this issue. (2.) I would have like to have seen some discussion about the uncertainty of the correct metric to consider for diesel exhaust. Total mass is emphasized at present. Uncertainty exists about issues such as particle number and surface area as well of chemistry. (3.) The classification argument should also make use of the fact that diesel exhaust contains known carcinogens. What is the EPA position about mixtures containing carcinogens; i.e., if a mixture contains a known carcinogen, is the mixture automatically a carcinogen?

Specific comments: Section 8.2.1: I personally am not supportive using comparative potency methods to derive unit risk estimates of carcinogenicity. Such estimates are highly sensitive to the biological (assay) endpoint chosen as well as to the dose/exposure level at which the biological/assay result was derived. I would like to see this section criticized more heavily; others, however, may disagree with me. It is noteworthy, however, to state that this method is not consonant with methods used or proposed in EPA's Risk Assessment Guidelines.

Section 8.2.6.1: I would like to see this section expanded to present more details of the various analyses. Such an expansion would, however, be more appropriate in Chapter 7.

p. 8-13, l. 32: Delete "highly"; see above.

p. 8-14, ll. 9-11: Either support this statement or delete it.

l. 19: This is likely an oversimplification because it considers the lowest exposed group in the Steenland study; is there evidence of increased cancers among this group; if not, delete this statement.

ll 26-33: I would delete this paragraph.

p. 8-16, l. 10: Delete "highly".

Chapter 9: Overall comments: (1.) This chapter is very useful and is more appropriately placed at the end of the document. (2.) Delete the word "highly" in describing the carcinogenicity of diesel emissions. See my above comments. (3.) Linkages with the PM health effects literature need to be strengthened.

Specific comments: p. 9-1, l. 15: The wording is curious; can something more scientific be given in place of "that raise suspicions".

ll. 18-20: Somewhere is this document this issue should be discussed in more detail then referenced here. See my above comments.

l. 27: Be more specific; "of interest" says nothing.

ll. 28-32: Link this to the PM health database.

p. 9-2, l. 25-28: The definitions are not consistent with those that EPA has applied to the PM issue, They should be consistent.

p. 9-3, l. 18: Are these all likely to be on the surface of particles?

p. 9-5, ll. 7-8: The significance of this issue for risk assessment should be noted.

p. 9-6, l. 1: Is 4.4 really the lower bound?

ll. 1-7: Give time averages for all numbers.

p. 9-10, l. 13: Give averaging time.

ll. 22-23: Clarify; I don't understand the wording here.

p. 9-15, ll. 20-26: Delete. I have strong reservations about the value of these estimates.

Leslie Stayner

Chapter 6 - Non-cancer Dose-Response Evaluation

This chapter presents a rather straightforward NOAEL/Uncertainty factor analysis to derive an RFC for the acute effects of diesel exhaust. As the documents points out this approach is largely based on policy rather than science. I have just a few comments/concerns about the methodology used, which are listed below.

a) The uncertainty factor for animal to human extrapolation was reduced from the conventional factor of 10 to a factor of 3. The justification for this reduction was that a pharmacokinetic (PK) model was used for the extrapolation reducing a part of the uncertainty. EPA has partitioned the factor of 10 into a factor of 3 for PK, and 3 for pharmadodynamics. However, this correction in the uncertainty factor appears to rest on the assumption that the PK model does not have any uncertainty. I do not believe this is true for any PK model and certainly is not true in this case. The PK model used

was derived using data from rats, and simple assumptions about scaling to humans. Thus there was no human data used in developing this model, and the model itself is an extrapolation from animals to humans. In fact, research done in my branch by Dr. Eileen Kuempel (doctoral dissertation, University of Cincinnati, 1997) on the development of a PK model for coal dust suggests that this model is inadequate to describe dust retention in humans. Her research indicates that interstitial storage of coal dust is far more important than alveolar macrophrage clearance in humans, in contrast to rats who largely clear dusts through the macrophages. This is consistent with studies in primates. The PK model developed by Yu and Yoon that was used in this document does not include an interstitial department, and Dr. Kuempel found that similar models did not fit autopsy lung burden data for coal miners. In any case, if it is assumed that the PK component of -this uncertainty factor is a factor of 3 then it seems that an adjustment of less than 3 is warranted because of uncertainty in the PK model.

b) It is unclear why a benchmark dose analysis could not have been performed with the HERP or ITRI studies. The rationale offered on page 6-20 do not seem to make much sense. The fact that some studies did not have adequate quantitative data is true, but it does apply to the HERP and ITRI studies that did have quantitative data. The criteria for choosing from many endpoints should be same for the BMC approach is it is for the NOAEL approach. It would seem that the fact that a deposition model is available only for rats would be a problem for both approaches.

c) Page 6-13, lines 23-27: The choice of the NOAEL as the highest NOAEL that is below all the LOAELs presented in table 6-2 seems somewhat irrational. This approach would make sense if you were looking at the results from a single multi-dose study. However, in this case there are 3 different studies with different protocols and even different engine types. The ITRI study had a lower NOAEL (0.042) than the HERP studies, which may reflect differences in the nature of the exposure and not the level of the threshold.

d) It seems odd that a high level of confidence was assigned to this RFC which is based on crude analyses of animal data when there is little if any support for these effects from the epidemiologic literature. This judgement is in sharp contrast to the cancer dose-response assessment where there is abundant epidemiologic evidence, but the agency was not confident enough in the data to provide any estimate of unit risk. In any case, it would seem that the lack of human evidence for the acute effects would preclude the assignment of a "high" level of confidence in the RFC.

e) Page 7-138, lines 15-17: This sentence suggests that the rat appears to be more sensitive to the non-carcinogenic effects of diesel than humans. What is the basis for

this statement? If it can be substantiated it would imply that the factor of 3 for pharmacodynamics should be reduced.

Chapter 8 - Cancer Dose-response evaluations

This chapter presents a review of previous attempts by various individuals and organizations to determine a dose-response or rather a risk-response relationship for lung cancer and exposure to diesel exhaust particulates. The EPA has decided to not present any new analyses or to adopt the results from any previous dose-response analyses in this health assessment, or in other words has not decided on a "unit-risk" value. This decision was based on 1) the view that the toxicologic studies are unsuitable for quantitatively estimating human risks, and 2) there are still substantial and unresolved controversies about the analyses of exposure-response in the two available occupational epidemiologic studies.

This reviewer concurs with their decision to defer the presentation of quantitative estimates of risk for cancer pending the results from ongoing investigations by researchers at NIOSH and elsewhere. There are 2 important developments in the near that may impact our ability to estimate risk based on the available epidemiologic studies in the near term. The first is an update of the railroad workers study by Garshick et al. (1988). Subsequent to the publication of this study, it was discovered that there was a large percentage of missing deaths in the last years of followup of this cohort (1976- 1980). NIOSH has been working with Dr. Garshick to update his cohort with these missing deaths, and it is anticipated that this will be accomplished in the year 2000.

The second development is a joint effort by researchers at NIOSH and at the EPA's Division of Mobile Sources to develop revised estimates of historic exposure for the analysis of the truck driver cohort study by Steenland et al. (1998). Significant criticisms of the assumptions used in this analysis for estimating historic exposures were made in the recent review by the Health Effects Institute (1999) particularly about the assumptions concerning the emission factors of diesel engines over time. Working with EPA we have identified new data that we believe will permit us to develop improved estimates of the emission factors, and historical exposures for this cohort. We are anticipating that we will be able to refine these estimate of exposuro and repeat the exposure-response analysis in the year 2000.

It must be emphasized that we can not predict whether or not these new analyses will provide a better basis for quantitative estimates of risk until we have the results from these investigations. It is entirely possible that neither analysis will result in a positive or significant exposure-response relationship. Furthermore, it needs to be recognized that even if the results are highly positive, that in both studies there will remain significant uncertainties in the estimates of exposure, and hence the dose-response relationships. All that we can guarantee is that these analyses will be conducted using the most scientifically defensible methods, and that we will attempt to evaluate these uncertainties to the fullest extent possible.

The remainder of this chapter presents a summary of previous risk analyses that have been previously reported, and some discussion about the relevance of these analyses, and an attempt to put these risk estimates in perspective.

I have the following technical comments on the Chapter:

a) There is one approach to the risk assessment that was left out of this review, which is by California EPA who in their final document used the meta-analytic results from Lipsett et al. (1999) to estimate risk with crude estimates of occupational exposures. I personally believe that this approach has considerable merit at this time until we have better dose-response information.

b) Section 8.3. Observations of Risk (Page 8-13 to 8-15). This section makes what I think is a very important point, which is that although we can't accurately quantify the risk, it would appear that it is at least of regulatory concern by EPA standards (i.e., the risk is > than in a million). Unfortunately, I don't think this paragraph makes the case very clearly. I would suggest one could make the case in the following way. If one accepts that the epidemiologic evidence is causal and the excess relative risk observed in these studies is roughly about 40% this can be used to crudely estimate lifetime risk. The lifetime risk of lung cancer in humans is approximately 3 %. Thus a 40 % excess risk would correspond to an excess lifetime risk of approximately 1 percent or 1 per 100. If the high end of environmental exposures is less than a factor of 10 than the occupational exposure levels in the epidemiologic studies (as the current text implies) then if one assumes a linear dose-response relationship the Lipper end of environmental risk may approach 1 per 1000. In any case, the environmental risks would be greater than the 1 per million threshold level that EPA generally considers of regulatory concern.

c) Page 8-1, lines 17-18: This sentence defends the use of older toxicologic studies for quantitative risk analysis (ORA). However, the first sentence of this paragraph suggests that the tox studies should not be used in any case for QRA. Perhaps the word epidemiologic should be substituted for toxicologic.

d) Page 8-5, last line: I would suggest adding "in rodents" to the end of this sentence. We don't know if this statement is true for humans,

e) The unit risk estimates presented from Smith and Stayner (1990) and Hattis and Silver (1994) were for occupational exposure scenarios and need to be adjusted for environmental exposure scenarios. The Smith and Stayner estimates are reported as upper bound estimates, but this paper only reported point estimates. Hattis and Silver

also reported risk estimates for smokers that were - substantially higher (22×10^{-5}), which should be included in your table and summary.

f) Page 8-7, 2nd paragraph: It is suggested that there are 2 major sources of uncertainty in using the animal bioassay data. However, the second one (shape of the dose-response) seems to be moot given the acceptance by EPA of the first (inadequacy of the rat model for quantifying human risk). In discussing the issue of coal, it should be pointed out that the relevance of this example is extremely limited by the fact that coal dust is a much larger particle than diesel. I believe there is also a study of German coal miners by Morfeld that shows an excess of lung cancer. Moreover, if one is going to discuss coal as an example why not discuss silica or asbestos as examples where humans appeer to be at least as sensitive as rats.

g) Page 8-10, line 3: An excess of 100 to 400 deaths among how many people and what level of exposure? This sentence is meaningless as written.

h) Page 8-1 0, line 22: The estimated risk presented was for truck drivers and probably is irrelevant here. A unit risk estimate for this study was presented in the companion paper by Stayner et al. (1998), which was 0.45×10^{-3}. This estimate is probably preferable for this presentation, although it would need to be adjusted for environmental exposures.

i) Page 8-1 1, first paragraph: The first sentence seems to be missing something. Perhaps you should substitute the word "that" for the word “but”. Third sentence needs to be rewritten. It seems like to sentences were combined. The study by Sagai does not seem relevant to the argument being made in this paragraph, since it suggests a particle effect for diesel and this paragraph is arguing that there could be non-overload effects involving the organic fraction.

j) Page 8-1 1, line 19 - I would suggest replacing "eliminate or reduce" with "control for”.

k) Page 8-12, line 11 - NIOSH is not funding an undercount of the Garshick data! NIOSH has funded an effort to obtain the death certificates to correct the undercount in the Garshick data.

l) Page 8-12 The discussion of the Crump and HEI analyses of the railroad workers study is very superficial and could be expanded.

m) Page 8-13, lines 14-15: The sentence doesn't make sense. What does a cumulative exposure mean for ambient air? Are you assuming 70 years of exposure? It seems that

a better way of making the point here would be to simply compare the range of average exposures in the truck driver study with the levels in the general population.

n) Page 8-14, last paragraph - This paragraph describes an additional risk analysis done by EPA in its last draft. It probably should be moved to the previous section that reviewed previous QRAS. It also seems kind of peculiar to use a previous draft of this document as a reference.

Other Comments

Page 1-3, lines 10-12: This sentence totally dismisses the relevance of the animal chronic bioassay studies relevance for predicting human cancer risk. This is inconsistent with other sections of this report that suggest that this information does have relevance for a qualitative determination of risk, but not for a quantitative risk assessment. I personally believe that at the very least the lung cancer excess in rat studies does add support to the positive lung cancer findings from the epidemiologic studies. I recognize some may argue that the mechanism in rats is related to overload, and that this mechanism would not apply to humans exposed to low levels of diesel. However, this assumes we have total confidence that the mechanism in rats has been established. There is at least 1 recent study that suggests that the organic, fraction may contribute to the carcinogenecity of diesel exhaust particulates. Futhermore, it is presumed that overload is not occuring in humans. Isn't it possible that some humans are already overloaded from other occupational exposures or personal habits (e.g., smoking). Isn't it possible that these individuals would be susceptible to the effects of diesel exhaust exposures even if overload is the mechanism?

Page 5-10, line 31-32: This sentence and several sentences in the review suggest that diesel exposure may be responsible for the increase in asthma incidence in the general population. This seems to be pure speculation and probably not realistic. Diesel exhaust exposures have decreased over the same time period that asthma incidence has been increasing. It would be sufficient to suggest that this and other studies indicate that exposure to diesel exhaust may be associated with an increased risk of asthma.

Page 5-94, lines I 0-1 9: This paragraph is a duplicate of a paragraph that appeared at the bottom of the previous page.

Page 7-39, lines 32-33: There is no OSHA standard for diesel exhaust. The sentence is probably referring to the fact that OSHA has generally regarded a 1 per 1000 risk significant for cancer and that the risk predicted was approximately 10 times higher than this level.

Page 7-54, lines 6-8: Publication bias has nothing to do with precision or study power. This sentence needs rewriting.

Page 7-71, lines 34-35: There was a recent study of German potash workers exposed to diesel exhaust that should be included in this review.

Page 7-72, lines 11-14: This paragraph dismisses the feasibility of conducting a study of diesel exposed miners. However, this is quite feasible and in fact NIOSH and NCI are currently conducting just such a study. The latency should not be too short with approximately 30 years since the introduction of diesel in the mines, and it has been possible to identify mines with little if any possible confounding exposures. The text probably should instead describe the current NIOSH/NCI study.

Page 7-79, first paragraph: The use of death certificates is not a major methodologic issue in these studies. The study by Percy discussed in this paragraph clearly suggests that lung cancer on death certificates is a relatively reliable source of information.

Page 7-81, lines 3-4: It is not appropriate to simply dismiss any study of lung cancer that does not control for smoking as this sentence suggests. Other aspects of the study design need to be considered. For example, if internal comparison groups are used then it is highly unlikely that smoking could be a strong confounder. Furthermore, one can examine other; smoking related causes of death in a SMR study and see if these causes are elevated or not. If they are not then it is highly unlikely that smoking is a confounder in these studies. In general, this document is far too dismissive of the epidemiologic studies with regard to this issue.

Page 7-84, line 1-1 2: The section on biologic plausibility should at least mention the lung cancer response in rats as another source of support. This can and should be said along with caveats about the issue of overload.

References

Garshick E, Schenkar MB, Munoz A, Segal M, Smith TJ, Woskie SR, Hammond SK, Speizer FE 1988. A retrospective cohort study of lung cancer and diesel exhaust exposure in railroad workers. Am Rev Respir Dis 137:820-825.

Stayner LT, Dankovic D, Smith R and Steeniand K. 1998. Predicted lung cancer risk among miners exposed to diesel exhaust particles. Am J Ind Med, 34:207-219.

Steeniand K, Deddens J and Stayner L. Diesel exhaust and lung cancer in the trucking industry exposure-response analysis and risk assessment. Am J Ind Med, Vol. 34:220- 228, 1998.

Roger O. McClellan

I am pleased to provide these written comments to complement the verbal comments I offered at the meeting on December 1, 1999 to review the latest "Health Assessment Document for Diesel Emissions". In my professional judgement the present document is not an adequate summary of the

available information for regulatory decision-malung and, hence, must come back to the CASAC in a revised form for review. The comments offered below are intended to aid in revising the document.

1 . General: One key issue with regard to the report is the statement of a hazard descriptor. I recommend the use of a descriptor as follows: "The existing evidence from the study of past sustained high level occupational exposures to whole diesel exhaust suggest that these exposures were likely carcinogenic to workers. Extrapolations from these exposures to generally lower ambient exposure levels provides suggestive evidence, but does not provide sufficient evidence, to characterize the human carcinogenic potential of current or projected ambient levels of diesel exhaust exposure. The present date base on past exposures and responses is not adequate to quantitatively characterize the carcinogenic risks of diesel exhaust exposure".

2. Chapter 3: Dosimetry: The chapter is headed in the right direction. It is important that it be better linked to the particulate matter criteria document and related papers. There is a critical need for quantitation with a comparison of expected deposition of diesel exhaust particles (perhaps at 1 microgram/cubic meter) to ambient levels of PM. The metric, micrograms/cubic meter, is an exposure index not a measure of dose. The document should more explicitly address susceptible populations, another area for linkage to the PM criteria document. It would also be useful to incorporate and reference the findings of the, recent ILSI Workshop on the overload issue.

3. Chapter 4: Mutagenesis: This chapter is on track and needs fine-tuning and integration. Individual studies are generally well described, however, the information is not always adequately integrated and interpreted. An example is the work of Driscoll et al. on carbon black and mutagenicity. This work needs to be placed in perspective. It is critical that the studies using extracts of diesel exhaust particles be placed in perspective as to the concentrations used compared to exposures of workers and laboratory animals and ambient exposures. I can provide a published figure to illustrate this point.

4. Chapter 7. Carcinogenicity: This chapter needs major revision to improve readability and to provide for more substantive interpretations of this literature. The format should be changed to provide an opening "road map" paragraph at the beginning of each major section followed by supporting detail. The tables should be placed at the beginning of each section and then the contents described.

The contents of the recent HEI report need to be more carefully considered in the EPA document. In my professional judgement the existing scientific data do not provide a basis for developing quantificative estimates of lung cancer risks attributable to ambient exposure to exhaust particles.

Specifically, it is not appropriate to use linear models of exposure- response relations to estimate either risks or associated cost benefits of exposure avoidance at ambient exposure levels. This viewpoint should be clearly articulated in the revised document.

Gunter Oberdörster

Review of Diesel Document, Chapter 4

General Comments - The previous review had raised a number of issues that were to be addressed in the revised draft. They are summarized as follows:

1. A quantitative integration of dosimetric information is needed to provide perspectives on the actual amounts of soot and soot-born compounds that will give rise to the doses to tissues and cells under environmental conditions.

2. The dosimetry chapter should include linkage to the dosimetry portions of the recent PM criteria document of the EPA.

3. The Discussion should also include more recent models for diesel soot dosimetry.

4. The large uncertainty in presently existing modern should be pointed out when extrapolating from rats to humans.

5. The discussion of particle overload is inadequate; the particle overload-induced lung tumors give a convincing argument against extrapolating the rat data to human cancer risk at environmental exposures.

6. Volatile and semi-volatile organics and gases were not included in the dosimetry chapter which needs to be addressed in the revised version.

Review of new draft, Chapter 4, Dosimetry: The revised version is significantly improved by responding to the comments of the reviewers and incorporating them into the revised version. The issues of doses to tissues and cells have been addressed to some degree (concepts are presented), and linkages to the dosimetry chapter of the PM criteria document are made throughout the revised chapter. More recent dosimetry models have also been incorporated, although the major emphasis is on the models by Yu and Yoon since this incorporates both the rat and human dosimetry for purposes of dosimetric extrapolation modeling. Attempts have also been made to address the uncertainty of the presently available models, and the discussion on the particle overload issue is much improved, although a most recent publication of an expert workshop on this issues has not been incorporated in this section (ILSI workshop on particle overload of March, 1998). The text is also more critical now with respect to extrapolating high dose-induced responses in the rat studies to effects to be expected from low environmental exposure levels. A section on organics has also been included, however, gaseous components of diesel exhaust are not considered in this chapter.

Specific Comments

Page 3-3, line 24: Aspect ratio is important for deposition by interception but not for impaction.

Page 3-7, line 18: Here and in several other places of this chapter the term "insoluble" should be replaced by "poorly soluble" or "particles of low solubility".

Page 3-8, line 1: I suggest deleting "for the most part" and include that the same clearance mechanisms act on specific particles to different degrees.

Page 3-9, line 2: Add to reference of Stahlhofen the ICRP 1994 reference.

Page 3-9, line 3: Add after "tracheobronchial region" the words "towards the larynx".

Page 3-10, lines 13 vs. line 21: The difference between the statement not to use intratracheal instilled particles (line 13) and the subsequent use of tracheal clearance after instillation (line 21) needs to be clarified.

Page 3-10, line 31/32: This statement is in contrast to page 3-13 where acceleration of tracheal clearance after high concentrations of DPM is reported.

Page 3-1 1, line 7: Change "deposited in" to "translocated to".

Page 3-12, line 18 - 25: An important study on retention of poorly soluble particles in humans by Bailey et al. (1985, Bailey, M.R., Fry, R.A., and James, A.C. Long-term retention of particles in the human respiratory tract. J. Aerosol Sci. 16: 295-305) is not included here. This study is the most comprehensive one on particle retention in humans, pointing out the importance of changing clearance rate over time such that particle retention halftimes vary from about 180 days at the beginning to 700 days later after deposition.

Page 3-12, line 33: Add after "lung burdens" the words "and estimated exposure histories".

Page 3-13, line 29: It is not clear why the intercept A would represent amounts cleared from the gastrointestinal compartment and why intercept B would represent intermediate clearance from the lung compartment and not the long-term clearance? This needs to be clarified.

Page 3-13, lines 33 and 34: This is a finding which contrasts previous statements (see comment above) that high doses of DPM may impair tracheobronchial clearance. This requires clarification.

Page 3-20, lines 29-32: This section does not appear to be very meaningful, stating that deposited particles may be either completely or incompletely cleared from the respiratory tract. If this section is retained, what should be included is a description of the changing pattern of the clearance over time as found by Bailey et al. (1985) (see comment above), and also that clearance kinetics are affected by total particle load (overload). Otherwise, it is not clear what this section is supposed to convey.

Page 3-20, line 36: Change "depends on" to "includes knowledge of'.

Page 3-21, line I 1: I suggest to change "retention of deposited particles" to "retained doses in the lower respiratory tract '.

Page 3-21, line 16: Delete the word "normal" and change "patterns" to "kinetics".

Page 3-21, line 26: It is not clear why the impact of respiratory disease would be especially in the tracheobronchial tree.

Page 3-22, lines 3-9: It would be desirable to include a reference to the recent ILSI workshop on particle overload which was held in March, 1998, with several participants from EPA. The workshop report is now in press in Inhalation Toxicology and has been distributed to all meeting participants. A definition of the particle overload phenomenon as well as other perfinent issues regarding particle overload-induced adverse effects have been presented at that workshop. For example, the term "overload" was defined as "For chronic inhalation of poorly soluble particles, particle overload is a consequence of exposure that results in a retained lung burden of particles that is greater than the steady-state burden predicted from the deposition rates and clearance kinetics of particles inhaled during exposure."

Page 3-22, line 16: This line ends with a sentence which is not finished and does not belong here.

Page 3-23, lines 7 and following: Morrow (1988) did not emphasize a concentration of 10 mg/lung as a lung burden at which particle clearance seizes, but rather emphasized the volumetric load of macrophages. This ought to be included here, rather than in the next section (page 3-24) since this is an important concept upon which also present occupational exposure limits to PNOC are based.

Page 3-24, line 1: Include the word "chronic" before "inflammation".

Page 3-24, lines 2 and 3: Change the orders of words at the end of the sentence and include mutational events as follows: ".....to the development of fibrosis, epithelial cell mutations and tumors in rats (Mauderly, 1996; Driscoll et al., 1996)."

Page 3-24, line 33 to Page 3-25, line 18: Move this portion to page 3-23 as pointed out above.

Page 3-25, line 27: Add the word "crystalline" before "silica" and delete the word "may". Also, another example of particles inducing impairment of lung clearance at much lower lung burdens is ultrafine particles as reported by Oberddrster et al. (1994 Inhaled Particles VU).

Page 3-27, line 36: Replace "aerodynamic" with "thermodynamic". Page 3-30, line 3: Add to end of sentence the words "in rats."

Page 3-32, line 32: Replace "half-life" with "halftime". The same applies to line 2 on Page 3-33.

Page 3-33, lines 4-11: This paragraph states that the deposition fractions for PM in the pulmonary and tracheobronchial regions of the human lung remain relatively unchanged for particles between 0.2 and 1.0 Fm. This is probably correct, and it would be useful to include a figure here like the one derived by ICRP in their recent 1994 model. Such figure should also show the range of predicted deposition efficiencies. It would also be useful to point out that the predicted particle deposition efficiencies for the different models can be quite different for specific particle sizes, i.e., differences between the NCRP and ICRP model or differences to the Yu and Dyu 1983 model. For example, a statement on lines 9 and 10 that deposition fraction in the pulmonary region increases significantly between 1 and 3.5 Fm is not supported by the ICRP model.

Page 3-33, line 14: Include after "transport rates" the word "were". Page 3-35, lines 2 and 3: Reference to the carcinogenicity chapter could be made here.

Page 3-36: With respect to the bioavailability of organics, the recent publication by Hiura et al. (Hiura, TS, MP Kaszubowski, Ning Li, and AE Nel. 1999. Chemicals in Diesel Exhaust Particles generate reactive oxygen radicals and induce apoptosis in macrophages.. J. Immuno. 5582-5591) should be included. This is a key paper which demonstrates the potential of diesel particle associated organics to induce oxidative stress in target cells. Diesel particles devoid of organics and carbon black or TiO_2 do not, showing that diesel particles, indeed, are different from other poorly soluble particles of low cytotoxicity. A caveat needs to be added, though, since the dose levels used by Hiura et al. (1999) for the in vitro dosing are very high.

Page 3-39, line 17: Organics eluted from the particles not only rapidly enter the blood stream - which is probably not the most likeliest event - but they are metabolized in specific cell types like Clara cells, type 11 cells and endothelial cells, either by inducible enzymes or enzymes already present, e.g., P450.

Page 3-39, line 27: Exchange "dose" with "exposure".

Page 3-40, line 3: Delete "insoluble or".

Page 3-41, lines 1-5: The statement that a greater percentage of diesel particles are deposited in the branching of small airways of laboratory primates is not described in the text preceding this summary of this chapter. The statement that eluted organic carcinogens remain in the lung long enough to be metabolized needs to be expanded on in the text on page 3-39 as commented on above.

Chapter 5: Mutagenicity In the previous review, it was suggested to include a discussion on the mutagenicity of particles with high doses without organic mutagens and also include a discussion of the mutagenicity from oxygen radicals which are thought to contribute to the lung tumor response of rats

after heavy high-level chronic exposures. Such discussion has not been incorporated in the revised chapter.

It was also suggested previously to discuss the issue of the high doses that have been used in mutagenicity assays. These doses are generally extremely high (e.g., 20 mg of DPM/hamster) and the relevancy of these doses to low environmental levels needs to be addressed. This has also not been done in the revised version.

Chapter 7.3: Carcinogenicity in Laboratory Animals

Specific Comments: Page 7-89: The study on top of page by Heinrich et al. (1989a) shows extremely high lung tumor incidences in controls as well as filtered and non-filtered diesel exhaust exposed animals. Is this correct? Also the superscript after PBN should be a lower-case d rather than lower-case c.

Page 7-121, lines 24-30: The issues of threshold needs to consider also additional information, for example, the correlation between the degree of inflammation and associated induction of mutations as shown in studies by Driscoll et al. support very well the existence of a threshold determined by the size of the inflammatory response. Thus, a number of data strongly suggest that, indeed, a threshold does exist.

Page 7-126, lines 19-31: The statement that the evidence for carcinogenicity of diesel exhaust is considered to be adequate from the animal studies needs to be qualified by emphasizing that it is by inhalation and in rats at high doses only. I don't think that the injection and skin- painting studies should be used to expand the evidence for carcinogenicity to include all animals. In the sentence of lines 26 and 27 of this paragraph, I suggest to include in the sentence with poorly soluble particles of carbon black and TiO_2 that long-term high exposure inhalation levels are required (change insoluble to poorly soluble).

Page 7-130, line 3: The study by Borm et al. should include also the dose levels to be used, were they very high compared to the *in vivo* situation?

Page 7-131, lines 5 and 6 and Page 7-132, line 14: I suggest including in the title of the sections discussing mechanisms of carcinogenicity the species from which this was derived, i.e., the rat.

Page 7-134: In this discussion of the importance of reactive oxygen species, the studies by Driscoll et al. (Driscoll, K.E., Deyo, L.C., Carter, J.M., Howard, B. W., Hassenbein, D.G., and Bertram, T.A. 1997. Effects of particle exposure and particle-elicited inflammatory cells on mutation in rat alveolar epithelial cells. Carcinogenesis 18 [No. 2]: 423-430) on the effects of particle exposure and particle elicited inflammatory cells on mutation in rat alveolar epithelial cells (Carcinogenesis 18, pg. 423, 1997) should be included. These studies show that particles co-incubated with lung epithelial cells do not induce mutations as co-incubation with ravaged particle-elicited inflammatory cells do induce such

mutations. Particles used were crystalline SiO_2, carbon black and TiO_2. These are key studies supporting the role of reactive oxygen species in inducing mutations in vivo (such in vivo mutations were also reported by Driscoll et al. after instillation as well as inhalation studies with carbon black) and they also show that the particles themselves do not have this interaction of mutagenicity with epithelial cells.

Page 7-135, lines 10 and 11: The statement that PMN levels are not excessive following the deposition of high lung burdens of TiO_2 in the Lee et al. study is not supported by data. Such measurements were not made in this study.

Page 7-135, lines 17 and 18: Driscoll (1996) performed a more comprehensive comparison of a number of inhalation studies correlating particle mass and particle surface area retained in the lung with tumor incidence and found that particle surface area is a much better dosimeter than particle mass.

Page 7-135, line 33: There is, indeed, good evidence that continued decrease in particle size into the ultrafine particle size range (20 nm, ultrafine TiO_2.) increases the carcinogenic and toxic potential of those particles. In fact, the study by Heinrich et al. with ultrafine TiO_2. can be compared to the study by Lee et al. with larger-sized pigment grade TiO_2 showing that in the Heinrich et al. study 10 mg/m^3 induced after two years of exposure higher incidence of lung tumors as did 250 mg/m^3 in Lee et al. study. Also, in the Heinrich study the niice exposed to the same concentration had to be taken out of the exposure because of the high apparent toxicity of these ultrafine TiO_2 after ten months of exposure. Thus, indeed, there is good evidence that the size of particles going into the ultrafine range is a very important parameter for toxicity and also carcinogenicity in the chronic exposure situation.

Page 7-136, line 10: I suggest changing "biochemically inert" to "low toxicity".

Page 7-137: In this figure, I think an important cell type, namely the neutrophils (PMN), are missing which are elicited via chemokines released from activated macrophages.
Driscoll et al. have shown that the PMNs are much stronger source for reactive oxygen species than macrophage are. Also added as an update to this figure should be organics which can elicit oxygen radical based responses (see paper by Hiura et al., 1999).

Page 7-138, line 21: Added to this sentence should also be a statement that this is also a phenomenon seen after longer exposures at high dose levels.

Page 7-139, line 1: For extraction of organics of retained particles, is it necessary to have available one year? Isn't the extraction process in the lung much faster?

Page 7-139, line 15: The statement that diesel engine exhaust is "highly likely" to be carcinogenic -needs to be followed by the modifier that this is only valid for high exposure concentrations over a long duration. Moreover, the sub-descriptor "highly" should be deleted since this may be misread as a quantitative assessment which has not been made at present.

Page 7-140, line 10: Add after "characterization" the words "if concentrations are very high".

Page 7-140, line 16: How small is the difference between higher and environmental exposure and occupational exposure levels?

Page 7-142, line 18: What is the evidence that diesel particles at low concentrations are ingested by epithelial cells and induce DNA damage?

Page 7-142, lines 23 and 24: What is the evidence for the statement that the resident time of organic compounds eluted at branching of small airways is increased?

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

REVIEW BY THE CLEAN AIR SCIENTIFIC ADVISORY COMMITTEE (CASAC)