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EPA CASAC REVIEW OF THE DRAFT DIESEL HEALTH ASSESSMENT DOCUMENT

REVIEW OF THE OFFICE OF RESEARCH & DEVELOPMENT'S DRAFT DIESEL HEALTH ASSESSMENT DOCUMENT BY THE CLEAN AIR SCIENTIFIC ADVISORY COMMITTEE (CASAC)

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

October 7, 1998

EPA-SAB-CASAC-99-001

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

OFFICE OF THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

Subject: Review of the Diesel Health Assessment Document

Dear Ms. Browner:

The Clean Air Scientific Advisory Committee (CASAC) of EPA's Science Advisory Board (SAB), supplemented by expert consultants (together referred to as the "Panel"), met on May 5-6, 1998 to review the February 1998 draft document, "Health Assessment Document for Diesel Emissions" (EPA/600/8-90/057C), 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 the 1995 draft and found it wanting. Specifically, the Committee concluded that the 1995 document was not scientifically adequate for making regulatory decisions concerning the use of diesel-powered engines. At the May 1998 meeting and in written comments provided to EPA staff, the Panel assessed the adequacy of the present draft as an accurate statement of current knowledge about the health effects of diesel exhaust inhaled in the environment, and made numerous suggestions for improvement. The determination of the Panel 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 EPA as a charge to the Panel.

It was the unanimous view of the Panel that the February 1998 draft is not an acceptable summary of current knowledge of the health effects of diesel exhaust inhaled in the environment, and thus, does not serve as an acceptable basis for regulatory decision making based on adverse health effects. The nature and magnitude of the draft's inadequacies precluded the choice of closing on the document pending revision.

Sections of the document, and especially the description of diesel engine emissions, are considerably out of date. The substantial differences between emissions from engines produced since the early 1990s and those to which human and animal subjects comprising our present health database were exposed was not portrayed. The document takes two approaches to using rat lung tumor data to develop quantitative estimates of human lung cancer risk from low-level environmental exposures. The majority view of the Panel was that neither approach is supported

rat lung tumor data to develop quantitative estimates of human lung cancer risk from low-level environmental exposures. The majority view of the Panel was that neither approach is supported by present knowledge of the nature and likely mechanisms of the rat response. The Panel noted that the above two issues repeat the two major criticisms of the 1995 draft; indeed, there has been no substantive updating of the emissions section since the 1990 draft.

The document failed to link the potential health effects and likely risks from environmental diesel soot to the effects and risks of airborne particulate matter, which were summarized and extensively reviewed and debated in conjunction with the recent review of the particulate matter standard. Through this lack, the document fails to make a clear case for treating diesel soot differently from the aggregate environmental particulate matter to which it contributes. Epidemiological data from occupational exposures are considered by the Panel to present the strongest current evidence for human cancer risk from inhaled diesel exhaust, although considerable uncertainty remains regarding the most appropriate use of these data. The present document falls short in its analysis of the exposure-dose-response relationships which are crucial for extrapolating from occupational to environmental exposure levels of soot and its potentially carcinogenic constituents. The absence of a convincing portrayal of the quantitative basis for extrapolation contributed to a division of opinion among the Panel as to whether a quantitative, in contrast to a qualitative, assessment can be justified at this time.

The Panel encourages the Agency to make a serious effort to develop a revised document that constitutes an acceptable statement of current knowledge regarding the potential health risks from environmental diesel exhaust. The Panel acknowledges that the task is difficult, but believes that such a document is within the Agency's grasp if sufficient attention is given to the above issues, the numerous written comments from the Panel, and the discussion recorded in the meeting transcript. The Agency is encouraged to engage CASAC in a discussion of its proposed strategy for remedying the document's deficiencies, prior to completing the next revision. The Panel looks forward to the opportunity to review and approve an appropriately revised document.

Sincerely,

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

NOTICE

This report has been written as a part of the activities of the Science Advisory Board, a public advisory group providing extramural scientific information and advice to the Administrator and other officials of the Environmental Protection Agency. The Board is structured to provide a balanced, expert assessment of scientific matters related to problems facing the Agency. This report has not been reviewed for approval by the Agency; hence, the comments of this report do not necessarily represent the views and policies of the Environmental Protection Agency or of other Federal agencies. Any mention of trade names or commercial products does not constitute endorsement or recommendation for use.

ABSTRACT

The Clean Air Scientific Advisory Committee (CASAC) of the EPA Science Advisory Board (SAB) reviewed the Agency's *Health Assessment Document for Diesel Emissions*. While acknowledging the difficulty of the task, the CASAC encouraged the Agency to revise the document, which the Committee judged to be not acceptable as a summary of the current knowledge of the health effects of diesel exhaust inhaled in the environment. Consequently, in CASAC's view, it does not serve as an acceptable basis for regulatory decision making, based on adverse health effects. The Committee's main concerns are as follows: a) Some of the information was judged to be considerably out of date. For example, the changes in diesel engines and their emissions that have occurred in the 1990s is not reflected in the document; b) Neither of the two approaches employed by the Agency to use animal data to generate estimates of human risks associated with environmental exposure to diesel exhaust was found to be supported by present knowledge; c) The document fails to distinguish the effects of diesel exhaust, *per se*, from the effects of $PM_{2.5}$ (particulate matter less than 2.5 microns in diameter), of which it is a constituent; and d) The human epidemiological data from occupational exposures present the strongest current evidence for human cancer risk from inhaled diesel exhaust. However, the Agency's document does not effectively address ongoing debates about the existing data. In the end the CASAC could not reach a consensus on whether a quantitative, rather than a qualitative, assessment can be scientifically justified at this time. This marks the second time that the CASAC has reviewed the Agency's health risk assessment of diesel exhaust. In its 1995 review, the Committee identified a number of shortcomings, some of which persist in the current document.

Keywords: Diesel Emissi. n, cancer risk, diesel exhaust, particulate matter

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

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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 May 5-6, 1998 to review the February 1998 draft document, *Health Assessment Document for Diesel Emissions* (EPA/600/8-90/057C), in a public meeting in Research Triangle Park, NC. This was the third draft of the document; preceding drafts were reviewed in 1990 (by an SAB Subcommittee) and 1995 (by an earlier CASAC Panel). CASAC found that the 1995 draft "was not scientifically adequate for making regulatory decisions concerning the use of diesel-powered engines". At the May 1998 meeting and in written comments, the Panel assessed the acceptability of the present draft as an adequate statement of current knowledge about the health effects of diesel exhaust inhaled in the environment, raising several key criticisms and making numerous suggestions for improvement.

It was the unanimous view of the Panel that the February 1998 draft is not an acceptable summary of current knowledge of the health effects of diesel exhaust inhaled in the environment, and thus, does not comprise an acceptable foundation for regulatory decision making on the basis of adverse health effects. The diverse nature and extensive magnitude of the draft's inadequacies precluded the choice of closing on the document pending minor revision.

The Panel found four key deficiencies in the draft. First, sections of the document, and especially the description of diesel engine emissions, were considerably out of date. The substantial differences between emissions from engines produced since the early 1990s and those to which human and animal subjects comprising our present health database were exposed was not portrayed. This had been a major criticism of the 1995 draft, and apparently no serious attempt has been made to correct that deficiency. Other areas needing updating included the current understanding of likely mechanisms of lung carcinogenesis in rats, and the current status of knowledge concerning the exposure-dose-response relationships among the epidemiological data. The Agency has not addressed the much-debated extent to which the current human epidemiologic database supports an exposure-response relationship between diesel exhaust and lung cancer.

Second, despite CASAC advice to the contrary in 1995, the Agency continues to use rat lung tumor data to develop quantitative estimates of human lung cancer risk from low-level environmental exposures. The present draft included two approaches, and the majority view of the Panel was that neither approach was supported by present knowledge of the nature and likely mechanisms of the rat response. Current knowledge comprises compelling evidence that the species-specific, overload-related rat lung tumor response to extremely high level exposures is not useful for estimating risk at environmental exposure levels, and is of doubtful relevance to

human risk from higher occupational exposures. The Agency also developed a quantitative risk estimate from potential rat tumor responses at lower exposure levels (still two orders of magnitude above environmental levels) using the highest response that might not have been detected because of the statistical power of the sizes of the individual treatment groups. The Agency justified this approach on the presumption of effects of the soot-associated organic compounds at low exposure levels. The Panel found no evidence supporting an effect of organic mutagens in the rat response at either the low or the high levels, and considerable evidence to the contrary.

Third, the document failed to attempt any linkage between the potential health effects and likely risks from environmental diesel soot to the effects and risks of airborne ambient particulate matter (PM). The effects of ambient PM were summarized and extensively reviewed and debated in conjunction with the recent review of the particulate matter standard. An important issue is whether or not diesel soot should be treated any differently than $PM_{2.5}$, of which it is a constituent. By failing to address this issue, the Agency did not make a case for treating diesel soot differently from $PM_{2.5}$ from a regulatory viewpoint.

Fourth, epidemiological data from occupational exposures were agreed by the Panel to present the strongest current evidence for human cancer risk from inhaled diesel exhaust, although the Panel noted that considerable uncertainty remains regarding the most appropriate interpretation and use of these data. The present draft fell short in its discussion and analysis of the exposure-dose-response relationships that are crucial for establishing a scientific basis for extrapolating from occupational to environmental exposure levels of soot and its potentially carcinogenic constituents. The continuing, unresolved debate on this topic was hardly mentioned. The Panel was disappointed that the Agency has not taken a lead role in resolving this issue, or by suggesting additional research that is needed to resolve it. There was an inadequate discussion of the amounts of mutagenic and carcinogenic exhaust constituents that would actually deposit in the respiratory tract during lifetime exposures. In part as a result of the lack of a convincing argument for a quantitative basis for extrapolation, the Panel remained divided as to whether a quantitative, rather than a qualitative, assessment can be justified at this time. No consensus was developed on this critical issue.

Numerous other important issues and additional more-minor points were raised by the Panel, and are contained in their individual written comments and the transcript of the meeting. The staff responsible for revising the document is strongly encouraged to review these sources of information in addition to the following summaries to gain the most complete perspective possible of the Panel's criticisms, and to contact Panel Members individually for clarification, if necessary. Regardless of the approach taken in its revision of the document, staff must make several key decisions in the face of continuing uncertainty. The Panel strongly encourages staff

to engage CASAC in a consultation on the strategy it proposes for remedying the document's deficiencies, prior to expending substantial effort in actually implementing the revisions.

Although acknowledging that the task is difficult, the Panel encourages the Agency to make a serious effort to develop a revised document that constitutes an acceptable statement of current knowledge regarding the potential health risks from environmental diesel exhaust.

2. INTRODUCTION AND CHARGE

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 prepared by the Agency's National Center for Environmental Assessment (NCEA) - Washington, DC Office. The Committee met May 5-6, 1998 in Research Triangle Park, NC.

This effort follows an earlier review 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).

For the present review, NCEA provided CASAC with a listing that identifies the disposition of the significant recommendations made by the Committee in 1995. This was provided to the Committee along with the 1998 version of the diesel assessment. 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 comments were submitted during the May 5-6, 1998 meeting and are part of the public record. The written comments, along with oral deliberations at the meeting, form the basis for the recommendations contained in this report. For completeness, we have included the individual comments of each panelist in Appendix A. Although a number of the comments are editorial, we believe that it is valuable to maintain a complete record of the peer review in this report.

2.2 Charge

A baseline CASAC review objective is taken for granted by NCEA (i.e., the adequacy of the assessment in identifying key hazard endpoints and characterizing the dose-response aspects pertinent to public health exposure according to EPA's guidance on assessing cancer risk and developing reference concentrations (RfC's). NCEA also asked that CASAC focus on several specific questions/issues.

a) For carcinogenic hazards and risk estimation purposes a key risk assessment choice is to decide whether the available evidence supports a nonthreshold hazard - low dose or threshold - higher dose hazard, or in the absence of definitive information whether rational inferences are more plausible one way or the other. Is NCEA's discussion of the topic and support for the position of an inferred nonthreshold - low dose hazard and risk, satisfactory?

b) NCEA discusses various approaches (and related uncertainties) in developing estimates of cancer risk.

   1) Does the equal mixing of approaches and the resulting risk values define a plausible range of risk estimates or is there a scientific case to be made that a subset of the estimates provides a more defensible basis for establishing a risk range?

   2) Do you find that the documents's discussion, or other insights the Committee might have, provides a basis for selecting a single or scientifically "best" estimate of cancer risk?

c) EPA's approach to characterizing the noncancer health hazards is to develop an "RfC" for diesel exhaust exposure. Do you find that our identification of the critical effects/studies and the selection of the RfC uncertainty factors (as allowed in the RfC methodology) is scientifically supportable and consistent with broader considerations of particle effects on humans?

3. DETAILED FINDINGS

3.1 Response to the Charge

On April 20, 1998, the EPA submitted a Charge to the Panel in the form of four questions concerning its approach to characterizing the potential health risks of diesel exhaust. EPA staff agreed at the close of the May 5-6, 1998 public meeting that the issues raised by the Charge had been covered during the discussion; however, there was not a focused attempt to provide consensus answers to the questions beyond the range of opinion expressed during the view of the document. The Agency is referred to the summary comments in subsequent sections as the most useful answers to the Charge.

3.2 Threshold vs. Non-threshold Approaches

The first element of the Charge asks

> *For carcinogenic hazards and risk estimation purposes, a key risk assessment choice is to decide whether the available evidence supports a non-threshold hazard - low dose or threshold - higher dose hazard, or in the absence of definitive information whether rational inferences are more plausible one way or the other. Is NCEA's discussion of the topic and support for the position of an inferred non-threshold - low dose hazard and risk, satisfactory?*

The Panel expressed concern that the discussion of threshold was not adequate. The Panel recognizes that there is no clear evidence for a threshold in the potential human lung cancer risk from environmental diesel exhaust. However, some panelists noted that there was not a sufficient scientific basis for assuming that lung cancer risk had no threshold; both regarding extrapolation from occupational exposure levels to the very low environmental exposure levels, and regarding the plausible dose of mutagenic organic material from environmental exposures. The discussion of the issue needs strengthening.

3.2 Developing Estimates of Cancer Risk

The second Charge element asks

> *NCEA discusses various approaches (and related uncertainties) in developing estimates of cancer risk.*

a) *Does the equal mixing of approaches and the resulting risk values define a plausible range of risk estimates, or is there a scientific case to be made that a subset of the estimates provides a more defensible basis for establishing a risk range?*

b) *Do you find the document's discussion, or other insights the Committee might have, provides a basis for selecting a single or scientifically "best" estimate of cancer risk?*

The Panel did not consider the different methods for developing quantitative estimates of cancer risk to be of equal value; thus, it was not comfortable with an "equal mixing" of approaches. For example, the Panel considered the estimates derived from rat data to be of lesser value than those developed using other methods. Both general and specific comments argued against portraying estimates derived by all approaches as a single range of estimates having equal validity.

Although there was a range of opinion regarding the validity of deriving any form of quantitative estimate of risk, as contrasted to a qualitative statement of risk, the Panel expressed a preference for using the epidemiological data if a quantitative estimate must be derived.

3.3 Using an RfC for Diesel Exhaust Exposure

The third Charge element asks

> *EPA's approach to characterizing the non-cancer health hazards is to develop an "RfC" for diesel exhaust exposure. Do you find that our identification of the critical effects studies and the selection of the RfC uncertainty factors (as allowed in the RfC methodology) is scientifically supportable and consistent with broader considerations of particle effects on humans.?*

There was considerable discussion about the value of calculating an RfC and the various uncertainty factors used in the document to derive the RfC. Although no consensus developed regarding the number and magnitude of the uncertainty factors, there was unanimous agreement that the draft document's discussion of the uncertainty factors was inadequate. Because of the lack of clarity about the basis and development of the uncertainty factors, it was not yet clear whether or not the derivation is scientifically supportable. The Panel noted that in this section, as throughout the document, there was an inadequate linkage of the information on diesel exhaust to the information on ambient particulate matter (PM) in general. The lack of rationale for an RfC lower than the 15 $\mu g/m^3$ annual $PM_{2.5}$ standard was noted by the Panel.

3.4 Comments by Chapter

3.4.1 Chapter 2 - Diesel Emissions

The Panel did not agree with the Agency's decision not to expend the effort to update this chapter on diesel emissions. The chapter must be updated in order for the document to be a credible statement of current knowledge. The fact that there are still 30-year old engines in use does not justify this decision. There are three interrelated key reasons, as well as several more minor ones, why this must be done: a) it is important to consider how changes in emissions might influence the nature of their toxicity and their potency; b) it is important to portray the differences between emissions from current production engines (i.e., the ones relevant to future risk) and those from engines to which the humans and animals comprising the present health database were exposed; and c) it is important, in the final analysis, to make a clear statement about whether or not the differences in emissions affect the value of the epidemiological data for assessing present and future risk.

This chapter should also include a discussion of the relevance of the exhaust dilution and measurement conditions used in the laboratory, and the resulting data, to the nature of exhaust actually inhaled in the environment. It should also include a summary of the diesel emissions control strategy and schedule that were presented orally at the meeting, and a projection of environmental exposure levels anticipated in view of the progressive controls.

3.4.2 Chapter 4 - Dosimetric Factors

This chapter fails to integrate dosimetric information into a coherent quantitative exposition of the deposition and disposition of inhaled soot. A quantitative integration would provide a much needed perspective on the actual amounts of soot and individual soot-borne compounds and classes of compounds that constitute the "doses" to tissues and cells under environmental exposure conditions. This discussion is important to the consideration of the plausibility of carcinogenesis from environmental exposures. This chapter should include linkage to the dosimetry portions of the recent PM Criteria Document (EPA, 1996). The Panel did not see any basis for taking a different approach to soot dosimetry than that taken for fine PM. The discussion should also include the more recent published models for diesel soot dosimetry (e.g., Stöber and McClellan, 1997).

The large uncertainty that presently exists in models used to extrapolate dosimetry from animals to humans is not adequately portrayed, and the discussion of the "particle overload" phenomenon, and its relevance to the high-dose rat diesel studies is inadequate. Properly reviewed, this information comprises a cogent argument against extrapolating high-dose rat lung tumor response to human cancer risk at environmental exposure levels.

The draft is not clear as to why non-soot exhaust constituents, such as volatile and semi-volatile organics and gases, are not considered in this chapter. Are they considered innocuous?

3.4.3 Chapter 5 - Noncancer Health Effects

As in other chapters, the lack of linkage to the recent PM documents is a significant deficiency. There is no discussion of the relationship between the potential health effects of diesel soot and the effects thought to result from exposure to ambient fine PM. The Panel views these as interrelated, rather than separate, issues.

The potential contribution of diesel exhaust to respiratory sensitization, amplification of allergic responses, and asthma, is very uncertain. While it is appropriate to mention this issue, the present draft overstates the present certainty of the relationship. The fact that diesel emissions have been falling while the incidences of asthma and rhinitis have been increasing is largely ignored. The chapter also gives a false impression that this is a recently emerging issue, by failing to note much of the earlier literature on the topic, including literature on the potential role of organic compounds. In addition, the bases and justifications for selecting the benchmark concentration and the interspecies uncertainty factor are not described clearly or argued convincingly.

3.4.4 Chapter 6 - Derivation of RfC Non-cancer Health Effects

The rationale underlying selection of the reference concentration (RfC) for diesel soot was not presented clearly or argued convincingly. The basis for selecting the benchmark effect level, and why it differed among health endpoints was not clear. The basis for the premise that humans are more sensitive than rats to non-cancer effects of diesel exhaust is unclear and unconvincing. It appears that the Agency changed its mind during the final stages of developing the document and gave different uncertainty factors in different chapters, demonstrating the Agency's own ambivalence on the issue and helping to fuel the Panel's skepticism.

Even after extensive discussion at the meeting, the Panel remained somewhat uncertain about the Agency's derivation of the RfC, and could not come to consensus regarding the most appropriate RfC. No clear guidance from the Panel emerged from the discussion. When polled, three panelists recommended setting the RfC at 15 $\mu g/m^3$, consistent with the annual standard for $PM_{2.5}$, three agreed that an RfC of 5 $\mu g/m^3$ was probably acceptable, but could neither understand in detail nor justify the method used to derive that value, two recommended giving a range of RfCs, and the rest abstained.

The Panel recommends that the Agency review its approach to this chapter and to calculating the RfC, giving consideration to this report and the individual written and oral comments of the Panel, and then discuss their proposed approach to the revision with CASAC prior to development of the next draft.

3.4.5 Chapter 7 - Carcinogenicity in Laboratory Animals

This chapter attempts to catalogue, but fails to integrate adequately, information from the animal carcinogenicity studies. Most relevant studies are correctly cited, but the information presented is inconsistent among the studies. Some very relevant studies are not cited; for example, neither the most extensive dose-response study of mice (Mauderly *et al.*, 1996) nor the most extensive study of DNA adducts in rats (Randerath *et al.*,1995) are described.

There was an inadequate effort to place the exposure material used in the studies in context. For example, it is not emphasized that all of the animal studies were conducted using old technology light- or medium-duty engines, and that no studies have been conducted using exhaust from railroad or marine engines. As another example, it is not noted that the titanium dioxide used in some studies had an ultra-fine particle size, while that used in other studies had a much larger particle size.

There is too strong an emphasis on reconciling the results among species. The lung tumor response clearly differs among the animal species tested to date and current evidence suggests that it may differ between rats and humans. The attempt to synthesize the existing data into hypotheses that unify the responses among species engendered unsupportable speculations.

The statement that there are not adequate dose-response studies in mice is erroneous. The Mauderly *et al.* (1996) dose-response study of mice was done in parallel to the study which is cited as one of the most reliable sources of dose-response data from rats, but the negative mouse study is not cited in the chapter.

This chapter does not contain an adequate analysis of the lung tumor data from rats exposed at the lower levels (still very high compared to environmental levels), nor does it contain an adequate discussion of the evidence concerning the effect of soot-associated organic compounds in rats at either high or low levels. These deficiencies lay the foundation for the questionable risk estimates that appear later in the document. The Panel viewed the premises that: a) a small tumor response at low exposure was overlooked due to statistical power; and b) soot-associated organic mutagens had a greater effect at low than at high exposure levels to be without foundation. In the absence of supporting evidence, the Panel did not view derivation of a quantitative estimate of human lung cancer risk from the low-level rat data as appropriate. The Panel noted that the aggregate data from several studies provide a useful test of carcinogenesis at

exposure levels two orders of magnitude above ambient, but give no suggestion of even an insignificant effect. The Panel also noted that there is no evidence that the organic fraction of soot played a role in rat tumorigenesis at any exposure level, and considerable evidence that it did not. However, the Panel also noted that the lack of organic effect in rats cannot be taken as proof that the organic fraction is not relevant to human risk.

3.4.6 Chapter 8 - Epidemiological Studies of Cancer Risk

The majority of the Panel were in general agreement with the final conclusion that there is limited evidence for a causal association between occupational exposure to diesel exhaust and lung cancer. The Panel was less supportive of either the utility of, or the basis for, the Agency's assertion that diesel exhaust was "close to being a known human carcinogen" within the present risk assessment framework.

The basis for selecting studies for presentation was not stated clearly. Several suggestions were made in the individual comments for presenting the studies in a clearer, more consistent manner, and some inaccuracies were noted in both the descriptions and the quantitative data presented. The discussion of the strengths and weaknesses of the individual studies should be strengthened, including the most likely duration of exposure in the different studies, the related issue of latency, and the likely importance of confounding in each study. Overall, the information in this chapter should be integrated in a more analytical manner.

This chapter does not contain an adequate discussion of the evidence for exposure-dose-response relationships between inhalation of diesel exhaust and lung cancer. Confidence that such a relationship exists is requisite for confidence in any extrapolation of cancer risk from occupational to environmental exposure levels. Much of the debate concerning the epidemiological data and their appropriate use has centered on this issue during recent years. Different investigators have analyzed the same data set and reached very different conclusions regarding the dose response for cancer risks from diesel exposure. The Panel found it disappointing that the Agency had not taken a lead role in resolving this crucial issue, and unacceptable that the chapter does not deal with this issue at all. The Panel recognizes that the issue may not be clearly resolvable at this time, but notes that regardless, our confidence in the quantitative risk assessment is directly proportional to the quality of our understanding of this issue.

3.4.7 Chapter 9 - Mutagenicity

The information on mutagenicity from organic compounds is presented well overall, and the chapter could be acceptable with attention to the following two issues:

a) The chapter needs to include a discussion of the current information from laboratory studies of mutagenicity from particles with high doses of poorly soluble particles of low cytotoxicity without organic mutagens. The alternate mutagenic pathways, such mutagenicity from oxygen radicals, which are now thought to contribute to the lung tumor response of rats to chronic, heavy exposures to particles should be discussed. This discussion will help place the rat results in their appropriate context.

b) The issue of dose is not discussed adequately. The doses of mutagenic material applied to bacteria and mammalian cells in the laboratory must be placed in context regarding the deposited doses that might plausibly result from human exposure to diesel soot in the environment.

3.4.8 Chapter 10 - Metabolism and Mechanism of Action

This chapter fails to pull the relevant information together into a cogent synthesis. The effort suffers from an apparent desire to reconcile results from animals and humans into a single, unified mechanistic framework. The existing evidence does not provide for such a reconciliation, and strongly suggests that if carcinogenesis occurs in humans, it occurs by mechanisms different from those responsible for the rat response.

It is considered most plausible that any human cancer risk from inhaled diesel exhaust would result from the mutagenicity of organic compounds absorbed in the respiratory tract. On this presumption, the issue of dosimetry of the organic compounds is crucial. The chapter does not give an adequate discussion of the actual doses of organic material likely to be absorbed from environmental exposures.

Present evidence does not support a role of organic mutagens in the lung tumor response of rats. Lung tumor and DNA adduct data from studies of rats exposed to diesel exhaust and other particles presents compelling evidence that the organics play no significant role at high exposure levels. There is no evidence for *in vivo* mutagenicity or DNA adduct formation in rats at non-overloading exposure levels. Present evidence suggests that carcinogenesis in rats is related to the inflammatory response and is likely mediated by oxidant injury. Discussion of this mechanistic pathway needs to be added to the chapter.

It is stated in this chapter and elsewhere in the document that exposure to diesel exhaust early in life, and especially from conception, is likely to render individuals more susceptible to exhaust. If no evidence can be cited nor a plausible mechanism given to support this assertion, it should be deleted.

3.4.9 Chapter 11 - Qualitative and Quantitative Evaluations of Carcinogenicity

There was a considerable range of opinion among the Panel regarding the derivation of quantitative estimates of human lung cancer risk from environmental exposures to diesel exhaust. That range of opinion is summarized in Section 4 (Conclusions) below. Staff is encouraged to read the individual written comments and the meeting transcript thoroughly to assess the many issues that were raised and suggestions for improvement.

Opinion was divided as to whether a quantitative risk assessment (derivation of a unit risk value) is justified at this time, or whether a qualitative statement is a more appropriate reflection of the current evidence for a likely carcinogenic effect at environmental exposure levels. In considering this issue, the Panel noted that the document does not describe the Agency's need for a quantitative risk assessment, or its intended use of a unit risk value unique to diesel exhaust particulate, and recommended that this information be added.

Consonant with the advice given to the Agency in 1995 (CASAC, 1995), the majority of panelists felt that the animal data should not be used to derive a qualitative risk estimate for environmental exposures. Several panelists felt that the laboratory results were useful for characterizing the carcinogenic hazard, and some felt that the animal data might be used in some manner to help frame cancer risk. Several other panelists noted that the issue of threshold had not been adequately discussed, and did not agree that present information supports a non-threshold linear extrapolation from occupational to environmental exposure levels.

The derivation and interpretation of the upper and lower bounds of risk need to be presented more clearly. There was considerable uncertainty among Panel members regarding the definitions of the bounds as presented in the chapter. Some preference was expressed for the use of maximum likelihood estimates rather than 95% confidence intervals for expressing the bounds of risk. It was noted that even if estimates from animal data were to be retained, it was not appropriate to combine estimates derived from human and animal data into a single range of risk.

3.4.10 Chapter 12 - Health Risk Characterization

The document states that this chapter is intended as a"lay" summary of the foregoing information and a summary synthesis of the health risks from diesel exhaust inhaled in the environment. The chapter falls short of accomplishing the former purpose. In several instances, the "simplified" language remains unnecessarily complex, and in others, it is misleading. The individual written comments should be reviewed for editorial suggestions. Figure 12 is too complex, especially considering the intended "lay" audience for this chapter. It was confusing to several panelists, and would not be useful for most lay readers.

The chapter does not give a straightforward, accurate view of the present large uncertainty regarding the cancer risk from environmental exposures. Characterization of environmental diesel exhaust as a "major" environmental hazard was considered by many panelists to be an overstatement. Because the chapter summarized the foregoing material, many of the criticisms of the preceding chapters were repeated for Chapter 12. Among the repeated issues were the failure to discuss technology-related changes in exhaust, the failure to tie diesel-health issues to PM-health issues, the inappropriateness of deriving risk estimates from the rat data, overstatement of the likely role of diesel exhaust in allergic disease, differences of opinion regarding the RfC, and lack of support for the assertion that exposures early in life render individuals more susceptible.

4. CONCLUSIONS

It was the unanimous view of the Panel that the February 1998 draft is not an acceptable summary of the current knowledge of the health effects of diesel exhaust inhaled in the environment, and thus, does not constitute an adequate basis for regulatory decision making based on adverse health effects. The nature and extent of the revisions needed are such that the Panel could not close on (approve) the document pending minor changes. It was agreed that a revised document must be re-reviewed by CASAC.

It was the consensus view of the Panel that the document must be revised to include an updated description of diesel engine emissions and the potential implications of changes in emissions for health risk. It was also the consensus view of the Panel that the document should link the discussion of the health risks from diesel exhaust to the health risks from PM, referencing the recent PM Criteria Document in the discussion of several issues. Finally, it was also the consensus view of the Panel that developing an acceptable document is a task within the reach of the Agency, but can only be accomplished if given more attention and resources than were evident from the advances made since the 1995 draft.

The range of opinions among the Panel on other major issues defy summarization as consensus views. Clearly, the Agency faces several difficult choices in revising the document. Although the Panel could not make consensus recommendations on several important points, two general recommendations are readily extracted from the discussion:

a) the Agency's choices regarding the portrayal and estimation of risk must be supported by scientific rationale that is clearly stated and must be defended on the basis of existing knowledge; and

b) the Agency would be well served by discussing their proposed approach to key issues with CASAC before completion of the next draft. For example, key issues might include the approach to discussing changes in exhaust, linkage to PM health risks and standards, derivation of the RfC, dose-response among the epidemiological data, approach to developing quantitative estimates of cancer risk (if done), and portrayal of the range of likely risk. The Panel recognized the Agency's desire for clear guidance on these issues, but developing consensus guidance was not possible within the framework of the document review and 1½ day meeting.

The range of opinion on certain issues was solicited by polling the 13 panelists at the end of the meeting. The following results might provide a useful perspective and illustrate the

uncertainty that exists in certain areas. The results should not be taken out of context as a "vote".

a) Recommend including some form of quantitative estimate of cancer risk?
Yes = 8, No = 3, Abstain = 2

b) Recommend using some form of animal data in estimating risk?
Yes = 5, No = 8

c) Continue to include an estimate based on benzo(a)pyrene?
Yes = 4, No = 4, Abstain = 5

d) Favor inclusion of comparative potency approach in general?
Yes = 7, No = 6

e) Develop quantitative estimate of risk from existing epidemiological data?
Yes = 8, No = 3, Abstain = 2

REFERENCES

Note: This list includes references suggested by the Panel as well as any references that are cited in the body of the CASAC report.

Baumgard, K.J., and J.H. Johnson. 1996. *The Effect of* Fuel and Engine Design on Diesel Exhaust Particle Size Distributions. Warrendale, PA: Society of Automotive Engineers; SAE technical paper no. 960131. Reprinted from Diesel Exhaust Aftertreatment 1996 (SP-1140).

Bagley, S.T, Baumgard, K.J., Gratz, L.D., Johnson, J.H., and D.G. Leddy. 1996. Characterization of Fuel and Aftertreatment Device Effects on Diesel Emissions. Health Effects Institute Research Report Number 76.

Begeman, C.R. 1962. *Carcinogenic Aromatic* Hydrocarbons in Automotive Effluents. Paper No. 440C presented January 1962 at the SAE Automotive Engineering Congress. SAE Technical Progress Series Vol. 6, "Vehicle Emissions", Society of Automotive Engineers Inc., New York.

Bjørseth, A., and A.J. Dennis. 1980. The problem of PAH degradation during filter collection of airborne particulates -- An evaluation of several commonly used filter media. Polynuclear Aromatic Hydrocarbons: Fourth International Symposium on Analysis, Chemistry and Biology, Battelle Press, Columbus, OH.

Boorman, G.A., Brockman, M., Carlton, W.W., Davis, J.M.G., Dungworth, D.L., Hahn, F.F., Mohr, U., Reichhelm, H.R., Turusov, V.S., and S. Wagner. 1996. Classification of cystic keratinizing squamous lesions of the rat lung: Report of a workshop. Tox. Path. 24(5):564-572.

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

Cass, G.R., and H.A. Gray. 1995. Regional emissions and atmospheric concentrations of diesel engine particulate matter: Los Angeles as a case study. In Diesel Exhaust: A Critical Analysis of Emissions, Exposure, and Health Effects. Health Effects Institute, Cambridge, MA p. 126-137.

Cuddihy, R.G., Seiler, F A., Griffith, W.C., Scott, B.R. and R.O. McClellan. 1980. Potential health and environmental effects of diesel light duty vehicles. DOE Research and Development Report, LMF-82. Springfield, VA: National Technical Information Service.

Davies, C.N. 1980. An algebraical model for the deposition of aerosols in the human respiratory tract during steady breathing-Addendum. *J. Aerosol Sci.* 11:213-224.

Dolan, D.F., Kittelson, D.B., and D.Y.H. Pui. 1980. Diesel Exhaust Particle Size Distribution Measurement Techniques. Society of Automotive Engineers; SAE technical paper no. 800187, Warrendale, PA.

Driscoll, K.D., Carter, J.M., Howard, B.W., Hassenbein, D.G., Pepelko, W., Baggs, R.B., and G. Oberdörster. 1966. Pulmonary inflammatory, chemokine, and mutagenic responses in rats after subchronic inhalation of carbon black. *Toxicology and Applied Pharmacology*, 136:372-380.

EPA. 1996. *Air Quality Criteria for Particulate Matter*. Office of Health and Environmental Assessment. Office of Research and Development, US Environmental Protection Agency, Research Triangle Park, NC.

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

Gertler, A.W., Sagebiel, J.C., Dippel, W.A., and R.J. Farina. 1998. Measurements of dioxin and furan emission factors from heavy-duty diesel vehicles. *J. Air & Waste Manage. Assoc.* 48:276-278.

Hampton, C.V., Pierson, W.R., Schuetzle, D., and T.M. Harvey. 1983. Hydrocarbon gases emitted from vehicles on the road. 2. Determination of emission rates from diesel and spark-ignition vehicles. *Environmental Science and Technology*, 17(12):699-708.

ICRP. 1994. Human Respiratory Tract Model for Radiological Protection, International Commission on Radiological Protection (ICRP66), ICRP Publication 66, *Annals of the ICRP* 24(1/3) 482 pp.

Kittelson, D.B., Kadue, P.A., Scherrer, H.C., and R.E. Lovrien. 1988. Characterization of diesel exhaust particles in the atmosphere. Final report to Coordinating Research Council AP-2 Project Group, March 1988.

Maejima, K., Tamura, K., Taniguchi, Y., Nagase, S., and H. Tanaka. 1997. Comparison of the effects of various fine particles on IgE antibody production in mice inhaling Japanese cedar pollen allergens. J. Toxicol Environ Health, 52:231-248.

Mauderly, J. L., Banas, D.A., Griffith, W.C., Hahn, F.F., Henderson R.F., and R. O. McClellan. 1996. Diesel exhaust is not a pulmonary carcinogen in CD-1 mice exposed under conditions carcinogenic to F344 rats. *Fundam. Appl. Toxicol.* 30:233-242.

McClellan, R.O. 1996. Lung cancer in rats from prolonged exposure to high concentrations of carbonaceous particles: Implications for human risk assessment. *Inhalation Toxicology* 8(Supplement):193-226.

McClellan, R.O. 1997. Use of mechanistic data in assessing human risks from exposure to particles. *Environmental Health Perspectives*, 105(Supplement 5):1363-1372.

Miguel, A.H., Kirchstetter, T.W., Harley, H.A., and S.V. Hering. 1998. On-road emissions of particulate polycyclic aromatic hydrocarbons and black carbon from gasoline and diesel vehicles. *Environmental Science and Technology*, 32(4):450-455.

Moore, G.E., and M. Katz. 1960. Polynuclear Aromatic Hydrocarbons in the Particulates of Diesel Exhaust in Railway Tunnels and in the Particulates of an Urban Atmosphere. *Int. J. Air Poll.* 2, 221-235.

NFRAQS. 1998. Northern Front Range Air Quality Study. *EM*, January 1998, pg 13-19. (See http://charon.CIRA.colostate.edu).

Oberdörster, G., Ferin, J., Baggs, R., Pinkerton, K. and Morrow, P.E. 1997. Alveolar macrophage cluster formation: A clearance mechanism for large particles in mouse lungs. In: Inhaled Partices VII, ed. Cherry, N. and Odgen, T., Pergamon Press, p. 554-560.

Okamoto, W.K., Gorse, R.A., and W.R. Pierson. 1983. Nitric acid in diesel exhaust. *J Air Poll Control Assoc.*, 33(11):1098-1100.

Pfluger D.H., and C.E. Minder. 1994. A mortality study of lung cancer among Swiss professional drivers: accounting for the smoking related fraction by a multivariate approach. Soz Praventivmed; 39:372-378.

Pierson, W.R., Gorse, R.A., Szkarlat, A.C., Brachaczek, W.W., Japar, S.M., Lee, F.S.-C., Zweidinger, R.B., and L.D. Claxton. 1983. Mutagenicity and chemical characteristics of carbonaceous particulate matter from vehicles on the road. *Environmental Science and Technology*, 17(1):31-44.

Pierson, W.R., Gertler, A.W., Robinson, N.F., Sagebiel, J.C., Zielinska, B., Bishop, G.A., Stedman, D.H., Zweidinger, R.B., and W.D. Ray. 1996. Real-world automotive emissions -- summary of studies in the Fort McHenry and Tuscarora Mountain tunnels. *Atmospheric Environment*, 30(12):2233-2256.

Rafnsson V., and H. Gunnarsdottir. 1991. Mortality among professional drivers. Scan J Work Environ Health; 17:312-317.

Randerath, K., Putman, K.L., Mauderly, J.L., Williams, P.L., and E. Randerath. 1995. Pulmonary toxicity of inhaled diesel exhaust and carbon black in chronically exposed rats. Research Report Number 68, Health Effects Research Institute Research Report, Cambridge, MA, December, 1995.

Sagebiel, J.C., Zielinska, B., Pierson, W.R., and A. W. Gertler. 1966. Real-world emissions and calculated reactivities of organic species from motor vehicles. *Atmospheric Environment*, 30(12):2287-2296.

Salmeen, I.T., Gorse, R.A., and W.R. Pierson. 1985. Ames assay chromatograms of extracts of diesle exhaust particles from heay-duty trucks on the road and from passenger cars on a dynamometer. *Environmental Science and Technology*, 19(3):270-273.

Salvi, S.S., Blomberg, A., Rudell, B., Kelly F.J., Frew A.J., Hlgate S.T., and T. Sandstrom. 1996. Acute inflammatory response in the airways and peripheral blood after exposure to diesel exhaust in health human volunteers. Europ Resp J; 9(Supp 23):415S.

Scheuch, G. 1991. Die Dispersion, Deposition, und Clearance von Aerosolpartikeln in den menschlkichen Atemwegen (Ph.D. thesis), J.W. Goethe-Universität. Frankfurt am Main, Germany.

Scheuch, G., Kreyling, W., Haas, F. and W. Stahlhofen. 1993. Effect of settling velocity on particle recovery from human conducting airways after breath holding. *J. Aerosol Med.* 6(Suppl.):47.

Stahlhofen, W. 1989. Human lung clearance following bolus inhalation of radioaerosols. In: *Extrapolation of Dosimetric Relationships for Inhaled Particles and Gases*, pp 153-166, Academic Press, Washington, DC.

Stahlhofen, W., Gebhart, J. and J. Heyder. 1980. Experimental determination of the regional deposition of aerosol particles in the human respiratory tract. *Am. Ind. Hyg. Assoc. J.* 41:385.

Stahlhofen, W., Gebhart, J., Rudolf, G. and G. Scheuch. 1986. Measurement of lung clearance with pulses of radioactively-labeled aerosols. *J. Aerosol Sci.* 17:333-336

Stahlhofen, W., Gebhart, J., Rudolf, G., Scheuch, G. and K. Philipson. 1986. Clearance from the human airways of particles of different sizes deposited from inhaled aerosol boli. In: *Aerosols: Formation and Reactivity, Second International Aerosol Conference*, West Berlin, Germany, September 22-26, 1986, pp. 192-196, Pergamon Press, Oxford, U.K.

Stahlhofen, W., Gebhart, J., Rudolf, G. and G. Scheuch. 1987. Retention of radiolabeled Fe_2O_3-particles in human lungs. In: *Deposition and Clearance of Aerosols in the Human Respiratory Tract*, Second International Symposium, Salzburg, Austria, September 18-20, 1986, pp 123-128, (ed. Hofmann, W.) Facultas Universitätsverlag Ges.m.b.H. Vienna Austria.

Stahlhofen, W., Gebhart, J., Rudolf, G., Scheuch, G. and M.R. Bailey. 1986. Human lung clearance of inhaled radioactively labelled particles in horizontal and vertical position of the inhaling person, *J. Aerosol Sci.* 18:741-744.

Stahlhofen, W., Koebrich, R., Rudolf, G. and G. Scheuch. 1990. Short-term and long-term clearance of particles from the upper human respiratory tract as function of particle size. *J. Aerosol Sci.* 21(Suppl. 1):S407-S410.

Stahlhofen, W., Scheuch G. and M.R. Bailey. 1994. Measurement of the tracheobronchial clearance of particles after aerosol bolus inhalation. In: *Inhaled Particles VII, Proceedings of an International Symposium on Inhaled Particles Organized by the British Occupational Hygiene Society, 16-22 September 1991* (Eds. Dodgson, J. and McCallum, R.I.) *Ann. Occup. Hyg.* 189.

Stöber, W. and R.O. McClellan. 1997. Pulmonary retention and clearance of inhaled biopersistent aerosol particles: Data-reducing interpolation models and models of physiologically based systems. *Critical Reviews in Toxicology*, 27(6):539-598.

Swift, D.L., Montassier, N., Hopke, P.K., Karpen-Hayes, K., Cheng, Y-S., Su, Y.F., Yeh, H.C. and J.C. Strong. 1992. Inspiratory Deposition of Ultrafine Particles in Human Nasal Replicate Casts, *J. Aerosol Sci.* 23:65-72.

Tebbens, B.D., Thomas, J.F., and M. Mukai. 1963. Particulate Air Pollutants Resulting from Combustion. From ASTM Special Publication No. 352, Symposium on Air-Pollution Measurement Methods, presented at the Fourth Pacific Area National ASTM Meeting, Los Angeles, Oct. 5, 1962 (published 1963 by ASTM).

Truex, T.J., Pierson, W.R., and D.E. McKee. 1980. Sulfate in diesel exhaust. *Environmental Science and Technology*, 14(9):1118-1121.

Xu, G.B. and C.P. Yu. 1987. Deposition of diesel exhaust particles in mammalian lungs. A comparison between rodents and man. *Aerosol Science and Technology*, 7:117-123.

Zaebst, D.D., Clapp D E., Blade L.M., Marlow D.A., Steenland K., Hornung R.W., Scheutzle D., and J. Butler. 1991. Quantitative determination of trucking industry workers' exposures to diesel exhaust. Am Ind Hyg Assoc; 52:529-41.

Zielinska, B., Sagebiel, J.C., Harshfield, G., Gertler, A.W., and W.R. Pierson. 1996. Votatile organic compounds up to C_{20} emitted from motor vehicles; Measurement methods. *Atmospheric Environment*, 30(12):2269-2286.

APPENDIX A
Detailed Written Comments of Individual Panel Members

The following are the original, unedited written comments provided by individual Panelists prior to or at the May 5-6, 1998 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 May 5-6 meeting form the basis for this written report. (Note: these comments may contain uncorrected typographical errors that result from electronic translation).

Mauderly

GENERAL COMMENTS ON DOCUMENT

Overall, this document, "Health Assessment Document for Diesel Emissions", is not suitable for closure as presented. It requires substantial revision to constitute an acceptable statement of current knowledge about the potential health risks from airborne diesel engine emissions. The draft presented for review does not suggest that the Agency elected to put forth the effort necessary to develop an acceptable document. The panel's discussion with the Agency at the 5/5-6/98 meeting suggested that perhaps the effort expended reflects the Agency's own ambivalence about the purpose of, and thus the need for, the document. Progressive controls on diesel emissions are already in place, and will extend for several years into the future. It is not clear how directly this document would influence the Agency's decisions regarding diesel emissions.

The quality of the document received by CASAC is disappointing, particularly in view of the comments provided by CASAC in 1995. At that time, the principal criticisms were: 1) that several sections of the document were badly out of date; and 2) that it was not appropriate to develop quantitative estimates of human lung cancer risk from environmental exposures from the rat lung tumor response to high-level exposures. The approach taken by the Agency in developing the present draft conflicted directly with that advice. Although there are other problems with the document, those choices alone acted to ensure that the revision could not be approved by CASAC.

CHAPTER 1

GENERAL COMMENTS

None

SPECIFIC COMMENTS

P 1-1, last para: The paragraph beginning on line 31 doesn't make sense as written.

P 1-2, L 6-11: First, EPA has prepared two previous drafts of this document, so stating that it has never prepared a comprehensive health assessment document on diesel exhaust is misleading. This is certainly not a new effort, as the statement implies. Second, the abbreviation, "DE" has not yet been defined.

CHAPTER 2

GENERAL COMMENTS

This chapter presents a problem and forces a decision point. EPA has obviously decided that it is not necessary to update this information. While that position might be argued, no argument is presented, other than to say that there are still engines on the road built in the 70s and 80s. The material presented is dated to pre-1989, which is about 10 years ago. Engines and their emissions have evolved substantially during

that period. While it is true that there are old engines in use, the chapter certainly doesn't give a current perspective on the composition of diesel exhaust. It is not apparent that anyone was tasked with an update at all.

SPECIFIC COMMENTS

P 2-1, L 4-5: It is an understatement that the chapter does not reflect the most current literature. There are few references younger than 10 years old! No rationale is given for this choice. If the information is not worth updating, why is it worth including at all?

P 2-2, para 2: Why switch to using the terminology, diesel "oil" for fuel? That term is not used consistently.

P 2-2, L 12-31: Why include this information - is it relevant?

P 2-2, L 33-34: Presumably, diesel emissions also include products from whatever happened to be in the intake air as well.

P 2-2, L 40: The "LDD" and "HDD" abbreviations don't match those used on the preceding page.

P 2-4, L 10-22: These sections are repeats.

P 2-5, L 25-27: These CO values don't make sense as tailpipe emissions. Where do these concentrations exist?

P 2-5, L 31: Are the C-10 to C 25 MW molecules really "unburned diesel fuel"?

P 2-6, L 11-18: Carbon is still carbon, even if it is combined in different molecules. Carbon doesn't disappear during combustion. Presumably, the author is talking about elemental carbon.

P 2-7, L 15: The value of 0.5 m^3/g surface area seems small by a factor of 10. Is this a mistake?

P 2-7, L 27: What does "charged" mean here?

P 2-8, L 1: Give a reference for this statement.

P 2-8, L 14: First, state that the "soluble" extract is soluble in organic solvent. Second, why not call "diesel-generated particulate material" soot? Is it something besides soot?

P 2-10, L 6-18: First, the CO comparison must be with uncatalyzed engines. Do diesels produce lower CO than gasoline engines with catalysts? Second, what does

"average traffic" mean? Third, you are switching abbreviations again with HDD and LDD.

P 2-11: Why would we be interested in data this old? Have gasoline engine emissions not evolved since 1982?

P 2-12, second para: Are there no data for the U.S.? Why are we talking about gasoline engines in the U.K. in the 1980s?

P 2-12, L 30-33: Why use data from a foreign truck? What country did this come from? Are there no data for U.S. engines?

P 2-13, L 3: Are the evaporative and refueling emissions increasing as the statement implies?

P 2-14, Figure 2-1: This figure is 16 years old. What do contemporary data look like?

P 2-27, last para: I have heard Glen Cass talk during the past year about diesel-specific tracers. This paragraph suggests that there aren't any.

P 2-41, L 4: Not updating the chapter is highly questionable. Calling a 1988 reference "recent" is ridiculous! This suggests that the chapter hasn't even been read recently by the author.

P 2-43, L 7: I don't think "FTP" has been defined yet.

P 2-43, L 27: This statement indicates that ozone gets up to 1.5 ppm these days. Is that true?

P 2-47, section 2.5.1: I don't understand the value of this information if the traffic was only 5% diesel vehicles.

P 2-49, L 1: Why should we care about any data for which the portion of diesel vehicles is unknown?

P 2-56, first 2 paras: This has already been said - why repeat it here?

P 2-56, L 35: It should be made clear whether this is a U.S. average concentration, or whatever. The term "integrated" doesn't make it clear.

P 2-57, L 5: First, "Cal-EPA" has not been defined. Second, what kind of locations were the "three locations"?

P 2-57, para 3: Why mention dioxin? First, dioxin was not discussed previously as a diesel engine emission. Second, the cited facts are "unpublished".

P 2-58, para 1: This is not an adequate rationale for the decision not to update the chapter. Not only is the question of changing emissions "not rigorously addressed", it isn't addressed at all in any meaningful way. This isn't acceptable. While older engines are still on the road, newer ones are as well, and in ever-increasing numbers.

P 2-59, L 7-9: What about hopane as a marker? Do you disagree that it is one?

CHAPTER 4
GENERAL COMMENTS
The use of the rat in justifying the dosimetric approach seems weak at best. You discard the importance of vapor-phase compounds because they don't cause tumors in rats. You discard aldehydes because no nasal tumors were seen in rats. You note that rat lung tumors occurred only under 'overload' conditions, which you didn't define, and that soot-associated organics don't seem to be important for the rat response. The entire rationale based on rats seems circular

Why not just go back to basics. The present concern for diesel soot-induced carcinogenesis in humans is based solely on the soot-associated organics - it's as simple as that. Who needs the rat to justify soot as the proper dose indicator? Given that, you still need a better rationale, and perhaps some further thinking, about why you don't care about volatile organics. Are you really prepared to say that there are no environmental health issues associated with the volatiles?

This text indicates that, while you acknowledge the lack of utility of the rat lung tumors, your thinking is still being driven by the rat results to an inordinate degree.

Why not just defer to the recent PM criteria document for the particle dosimetry discussion, and just summarize a few key points here? There is no need to repeat it.

Regardless of the comments above and below, this chapter isn't in bad shape, and can be accepted with minor editing.

SPECIFIC COMMENTS
P 4-1, L 8-9: It is not clear what is meant by 'tumorigenic mechanisms' are 'dosimetric factors'.

P 4-1, para 2: Here you dismiss vapor-phase compounds because they don't cause tumors in rats. How do you know they aren't important in humans?

P 4-1, L 22: You'd better define 'particle overload' if you are going to use it. In line 29,

you switch to the term 'pulmonary overload'. Although neither is defined, you complicate things further by switching terms.

P 4-2, section 4.2: Why is the recent PM criteria document not cited for dosimetry information?

P 4-4, L 7: There are more recent reviews of dosimetry.

P 4-5, Figure 4-1: First, these data don't look to me like they represent current thinking. Do they? Second, Why use the 'M' symbols in the headings? Just write out what they mean. Third, the symbols listed in the third line of the footnotes aren't useful unless they are defined.

P 4-6, para 2: This isn't clear. What is meant by the statement that the 'deposition rate' will 'initiate particle redistribution'?

P 4-7, L 3-4: Under more or less continuous deposition conditions, the fact that organics might be released more rapidly from soot than previously thought doesn't necessarily make them less important.

P 4-11, L 26: Do you really mean that 'deposition' in the alveolar region was 60 mg, or was that the lung burden? Deposition and lung burden are quite different things.

P 4-14, L 17: I think you mean macrophage 'pool', not 'tool'.

P 4-15, figure 4-4: This figure is not useful without explaining all the symbols, which would be more than the reader wants, or needs. Take it out.

P 4-16, L 7: Do you really mean to say that the clearance impairments caused by silica are likely to be caused by surface-associated organics? If that's really what you meant to say, you'd better give references.

P 4-27, L 14-15: While the statements in the paragraph might be true, how does the last statement follow from the preceding statements?

P 4-28, section 4.4.4: Don't forget that soot gets into epithelial cells as well. In fact, it is possible that only the soot in epithelial cells is the 'effective dose'. That may not be true, but you can't summarily dismiss the possibility without mentioning it.

P 4-29, L 21: Capitalize 'Beagle'.

P 4- 31, L 17-18: Why are you concerned about 'overload' dosing regimes regarding

human risk?

P 4-33, L 4: Don't you mean 'organic matter dissociated from particles', rather than 'particle-free organic matter'? The latter would presumably be volatile organic matter, and you weren't worried about that earlier.

CHAPTER 5
GENERAL COMMENTS

This chapter ranks among the top in terms of being in acceptable shape. It could be accepted with relatively minor effort. The only general issue regards the section on immune responses. That section doesn't portray the issue of the specificity of the effect of diesel soot. While it is true that soot has adjuvant properties, it is not clear that this effect differs from that of other particle types. There is a Japanese study (Maejima et al. J Toxicol Env Health 52:231, 1997) which addressed that issue, and found that diesel soot was about average among several diverse particle types. That study is not referenced.

SPECIFIC COMMENTS

P 5-1, L 15: How can 100$\mu g/m^3$ be called a 'low' level?

P 5-2, section 5.1.1.1.1: While odor is a problem, The information isn't very useful unless information can be provided comparing detectable odor levels to concentrations of soot in units used elsewhere in the document.

P 5-6, L 18: A new paragraph should start in the middle of this line.

P 5-6, L 30: What was the challenge dose?

P 5-7, L 9-11, and 25: DAM may act to enhance allergic disease, but it is important to place DAM in the context of other particles. Some mention should be made of the issue of specificity.

P 5-18, L 3: Something is missing in the dosing description. How do you administer mg/kg 'for 30 min'?

P 5-18, L 10: What does 'potently' mean? How big were the increases? Potent compared to what?

P 5-25-26, Table 5-3: First the table lists the high exposure concentration in the Mauderly et al. 1987 study as 7.0 mg/m^3, when it was actually 7.1 (7.08). It is listed correctly in the text. Second, the Mauderly et al. FAAT 30:233, 1996 paper on mice is not included. It has data on body weight and survival.

P 5-31, Table 5-5: Again, the high dose in the Mauderly et al, 1987 study is listed incorrectly.

P 5-35, Table 5-6: Again, the Mauderly et al., 1996 mouse study is missing.

P 5-41, L 25-26: The sentence beginning 'although the mouse lungs' is not clear. Perhaps 'high' is meant to be 'higher'.

P 5-45, para 1: This summary doesn't mention the possibility of soot in epithelial cells being a problem.

P 5-51, para 3: Here the high dose in the Mauderly et al. 1987 study is listed incorrectly as 7.0 instead of 7.1 mg/m^3.

P 5-76, L 15-16: Here, you switch from calling the rats 'young' to calling them 'neonatal'. Which is correct?

P 5-77, L 22: It should be 'aggregation of macrophages in rats'.

P 5-78, para 1: It is arguable whether or not a 2-yr exposure of monkeys should be called 'chronic'. The point is well-taken that 2 yrs is a much smaller portion of the lifespan in monkeys than in rodents, and that a 2-yr study in monkeys is not an adequate carcinogenesis bioassay. However, a 2-yr exposure is still 'chronic' in the sense of time, in the parlance of bioassays.

P 5-84, L 6: Again, it is not at all clear that one would call a study of the same length 'chronic' in rats and 'subchronic' in monkeys. Better to avoid this jargon.

CHAPTER 6
GENERAL COMMENTS
This chapter is in reasonable shape, and can be accepted with attention to the minor points listed below.

SPECIFIC COMMENTS
P 6-1, L 27: 'RfD' should be 'RfC.

P 6-2, L 10: It hsould be -'risk values', rather than '-risk assessment values', unless you mean something that I don't understand.

P 6-3, L 7: There is high confidence that diesel exhaust can be a respiratory hazard at occupational exposure levels, but one can hardly have 'high' confidence that it is a hazard at environmental exposure levels.

P 6-5, paras 2-3: Who cares about the 'target concentrations'? You don't make that distinction elsewhere. Just list the actual exposure concentrations as you do elsewhere.

P 6-6, L 20: I don't recall that the abbreviations for the respiratory function parameters have been defined. They aren't used repeatedly, so just spell them out.

P 6- 6, para 4: Again, the high concentrations in this study were 7.1 mg/m3.

P 6-27, L 3: The concentration in the ITRI study was 0.35, not 0.36 mg/m3.

CHAPTER 7
GENERAL COMMENTS

The descriptions of the studies are highly variable, to the degree that it appears as somewhat of a ôrandom walkö. It is true that the reports of the studies varied in their detail, but it would be desirable to present them is some logical order and with some uniformity in describing the features of the methods you think are important for the reader to understand. The studies are not presented in alphabetical or chronological order. The following characteristics are presented for single studies, even though in some cases, the information is available for other studies as well. These comments will not be repeated below - look through the text and you'd find them:

Hours of day animals were exposed
Temperature and relative humidity in chambers
Rate of diluting airflow
Exposure during darkness
Tumor rate 'beyond that expected for aging F344 rats'
Number of engines used
'Lifetime' exposures (none were)
Trade name of carbon black used
Data for tumors at different interim sacrifice times

It is stated that positive studies included a postexposure observation period. Few did.

Squamous keratin cysts (or whatever you choose to call them) are not differentiated from other lesions in this chapter. That was a major criticism raised in the last review of the document. The type of lesion is listed for some studies in the tables, but no distinction is made in the text.

It is stated that exposure-response comparisons can't be made for mice (like they can for rats) because the experimental designs differed. That isn't any more true for mice than for rats. The problem with presenting exposure-response plots for mice,

is that there weren't positive responses to plot in the long-term studies.

SPECIFIC COMMENTS

P 7-1, para 1: Why repeat this material?

P 7-1, L 22: These emphases are hardly 'recent'.

P 7-9, Table 7-1: No group sizes are given for the Mauderly et al. Mouse study. They were presented clearly in the publication.

P 7-12, L 19: While it is true that the results indicated that the organic fraction was not the ôsole causeö of the tumors, that is a very biased description of the results. The results indicated that the organics played little, if any, role at all.

P 7-20, L 19-20: First, the numbers of animals listed are not the numbers examined for tumors, which would seem to be the more important number to list. Second, the high exposure level is incorrectly stated. It was 7.1 mg soot/m3, not 7.0.

P 7-21, L 1-5: In three different places in five lines, the population was described as 'animals', 'combined males and females', and 'males and females'. Are these all the same? Why the different terminologies?

P 7-23, L 31: True, 1986 is 'more recent' than 1982. In 1998, however, that hardly seems worth pointing out.

P 7-28, L 8: Why mention that this material was 'lampblack'? Carbon blacks come in several forms and are made by several processes, such as 'channel black'. You don't mention which kind of process was used when you cite other carbon black studies, so why here?

P 7-35, L 22-23: Your treatment of this information is not clear. You state that this study shows that diesel soot extracts are not effective tumor initiators or promoters, but you certainly assume they are in the rest of the document. It's not clear how you discard these findings without explanation.

P 7-39: The negative Mauderly et al. 1996 study is missing here. Any reason why it isn't relevant to the discussion?

P 7-43, figure 7-1: This figure isn't useful without taking the control tumor incidences into account some way. For example, why not use the net incidences (exposed minus control)?

P 7-44: Why are the Heinrich et al. 1995 and the Nikula et al. 1995 studies not

relevant to this discussion?

CHAPTER 8
GENERAL COMMENTS
It is only partially clear why the authors selected the particular studies for presentation. Some rationale is given for excluding other studies, but studies are still presented an then judged as useless for answering the issues. It seems like you either have to include them all, or excluide all except those you consider to present useful information.

It is not useful to switch back and forth between the terms 'exhaust' and 'fumes'. Technically, the two are not the same thing. Even though the original authors of the papers cited may have used the term 'fumes', there is no reason EPA has to perpetuate the mistake and confuse the reader.

The point is made in one place that some of the 'nonexposed' population might have nonoccupational exposures to diesel exhaust. While true, the point as presented is absurd. All subjects in the control groups, occupationally-exposed groups, and indeed in the entire U.S. population are exposed frequently, if not continuously to diesel exhaust. Indeed, they are all incurring the full range of effects that EPA proposes might result from environmental exposures. The studies only deal with presumed differences in the level of exposure, not with exposed and unexposed populations.

SPECIFIC COMMENTS
P 8-1, para 1: Why reiterate this information?

P 8-1, L 17: No study has been 'definitive'. What is meant here?

P 8-1, L 20: Exposure is 'uncertain' in all studies. What's the point?

P 8-2, L 8: Why use the term 'fumes'? I suppose in this case the idea was that the original authors used that term and the heading reflects the title of the paper.

P 8-4, L 26: Do a universal search on the chapter for the term 'dose-response'. None of the studies gave 'dose-response' information. All they gave was exposure-response information.

P 8-5, L 11: Who cares that the term 'rolling stock' was used? Why is this an important detail?

P 8-9, L 13-14: There are actually no exposure histories for any study. It is incorrect to state that this, or any other, study has 'limited' information on exposure level. None of them have any information on exposure level, do they?

P 8-30, L 23-25: It is not at all clear why comments are made as to how the study could have been improved. One could make that comment about all of the studies in the entire document, assuming that none were perfect. Making this point here doesn't make sense.

P 8-33, L 29: Should the first word of the line be ôcarcinogensö instead of 'cancers'? How is one 'exposed to cancers'?

P 8-59, L 4: The point about some individuals being nonoccupationally exposed seems off the mark. Do the authors believe that anyone in the U.S. is not nonoccupationally exposed to diesel exhaust? Everyone in all the 'control' groups used in the epidemiological studies are exposed frequently to diesel exhaust, and presumably incurring all the health risks that EPA proposes might be associated with environmental exposures. The 'exposed' groups only have higher exposures.

P 8-59, L 20: What is meant by 'extract' here?

P 8-59, L 29: It is not clear how the original authors could have used the exposure information more 'quantitatively'. Here again, the authors offer retrospective advice that is meaningless.

P 8-63, L 11: Why is it 'interesting' that the main risk factor for lung cancer was cigarette smoking? That's hardly unexpected. What's the point?

P 8-66, L 19: These criteria don't 'define' causality at all, their fulfillment 'suggests' that causality is an acceptable working assumption.

P 8-67, L 4: Why call the 1995 publication 'recent'?

P 8-67, L 7: The word 'consistently' doesn't seem appropriate here. Although there is no question that the preponderance of evidence indicates that occupational exposure to diesel exhaust is associated with an excess of lung cancer, certainly not all studies reviewed by HEI showed that. The word suggests that the finding waqs 'consistent' among all studies, and it was not.

P 8-67, L 14: I′ m not confident that this is what 'specificity' really means by these criteria. The studies found lung cancer because that is what they looked for. The fact that cancer as an endpoint was identified doesn't equate to specificity of effect. Cancer is certainly not specific to diesel exhaust.

P 8-67, L 34-35: Vostal suggested that particles induce lung cancer nonspecifically in rats. The sentence implies that Vostal suggested that this effect might occur in humans, and he did not.

P 8-70, L 6: This sounds like EPA is inventing a new category; 'close to human carcinogen'. The rationale of the paragraph seems a bit overdone.

CHAPTER 9
GENERAL COMMENTS
This chapter is lacking mention of whether or not the mutagenicity of soot from newer engines is similar to, or different than, that of soot from the older engines from which these data were derived. The chapter is unacceptable without some mention of this issue. Otherwise, it's in pretty good shape.

SPECIFIC COMMENTS
P 9-3, L 19: The point is not whether or not the data are 'conflicting'. The point is whether or not present data indicate that exposures by inhalation produce urinary mutagenic activity. There is not a clear statement on that.

CHAPTER 10
GENERAL COMMENTS
This chapter does not present a very accurate view of the current understanding of the most likely mechanisms of diesel exhaust-induced carcinogenesis in humans and animals. The treatment of the issue of mutagenesis by particle-associated organics is especially confusing, because seemingly conflicting notions are presented. A large part of the problem seems to be the author's attempt to reconcile the human and animal responses. This is a futile task.

It is repeatedly proposed that the longer residence time of particles in humans would enhance the opportunity for mutagenesis by organics, but it is also stated that residence time does not influence adduct formation in animals.

Adduct formation information is used to support an action of organic mutagens, but there is not emphasis on the fact that there is very little information to date showing that the elevations of adducts observed in exposed animals are any different from those in controls. For the most part, elevations of adducts in the animal studies are increases in the concentrations of the same adducts that occur in controls, which does not support the idea that the adducts resulted from soot-associated organic compounds. One of the most intensive studies of this issue is not even cited in the chapter (Randerath et al. HEI Report No. 68, 1995).

It is repeatedly acknowledged that increases in lung tumor incidences only occur in rats under overload conditions, yet it is also repeatedly hypothesized that a tumor effect occurred, or must have occurred, at low doses, but that the studies were not robust enough to detect it. This ôphantomö tumor effect is a strange and unsupportable hypothesis. The studies were just as robust at low levels as at high levels. If the aggregate data from the many studies acceptable as bioassays are presented (which is

not done), it is clear that the data do not suggest an increase that simply failed to reach statistical significance. The data do not suggest an increase at all. There is no scientific basis for calculating a phantome low-dose effect, and even less for using that imaginary effect to calculate quantitative estimates of human lung cancer risk!

The premise that organics play a larger role at low exposure levels is asserted repeatedly. This hypothesis doesn't make much sense, and is not well-defended. It makes sense that, if there are two separate phenomena and one operates only at high doses, then the other would dominate at low doses. However, this doesn't mean that the second response is larger at low doses, it only means that it is relatively larger.

The chapter needs to be edited to clarify the species being discussed at each point. As presently written, information is blended across species carelessly. This is a major point, and there is simply no reason for the Agency to confuse it. We get lung tumors in rats at high doses. Our present understanding clearly points to the fact that this signal should not be used to estimate human risk. We do not get tumors in animals at low doses. We seem to get an increased risk among human exposed occupationally. It is most plausible that the increased risk among humans stems from the soot-associated organics. The animal response does not seem to be associated with soot-associated organics. We don't understand precisely why there is an apparent difference among species, but there is plenty of evidence indicating that there is. End of story. Trying to unify the responses across species at this time is neither necessary nor wise.

It is stated that tumors only occur in mice exposed from conception, but this does not agree with the description of mouse responses elsewhere.

SPECIFIC COMMENTS

P 10-1, L 11: The organic play a relatively greater role at low levels. We have no evidence that they have an absolutely larger effect at low levels than at high.

P 10-2, para 2: Why give the brand name for the carbon black here? That isn't done for other studies - even those described on the same page.

P 10-2, L 19: The Fraunhofer study did not examine the tumorigenicity of the 'carbon core' of diesel soot. They used carbon black, not the carbon core of soot.

P 10-2, L 23: There must be words missing from this sentence - it doesn't make sense.

P 10-2, L 31 and 33: In two sentences, you state both that the carbon black did, and did not, have organics. Care to select one? The truth is, as reported, that the carbon black did have organics, but very little and the material that was extracted had very little mutagenic activity.

P 10-3, L 2: Soot in lymph nodes was observed in all diesel studies; why mention it here if you aren't going to mention it elsewhere?

P 10-3, L 30: The term 'overload', while admittedly vague, is not used only in reference to retained mass or volume. If you are going to use this term, you'd better give your definition.

P 10-4, para 1: Why talk about specific surface area for this material if you aren't going to mention it for other carbon blacks?

P 10-4, L 20: What is the evidence that the organics play a 'minor' role in overload-induced carcinogenicityö in rats? Is there evidence that it plays any role?

P 10-4, L 31: The Nikula reference is not a good reference for the composition of diesel soot - it just quotes other papers. Many other authors have quoted the Opresko paper - why not list them as well, if you are going to quote Nikula?

P 10-6, L 7: What is the basis for the statement that slow release of organics ôpreventsö overwhelming of activating pathways? This isn't stated as a hypothesis, it's stated as fact. What is the reference for this fact?

P 10-6, L 9-13: The rationale here escapes me. What is the link between the fact that all particles tend to form aggregates in the lung and their ability to 'react' with surrounding lung medium ôwithout interferenceö from other particles? What point is the author attempting to make?

P 10-6, L 24-25: First, I don't think other chapters agree that tumors have only been observed in mice exposed from conception. Second, how might exposure from conception make mice ômore sensitiveö? Is there other evidence for that? What would the mechanism be?

P 10-7, L 5: What is the relevance of kinetics in rats exposed to 500 mg/m3 to possible kinetics in humans?

P 10-8, L 32: The observation is that most of the retained particles are in macrophages, not most of the 'deposited' particles.

P 10-9, para 3: First, what alveolar cells could form tumors other than Type II cells? This is the only alveolar type that has been known to form tumors from any treatment. Second, the point about the metabolic potential of Type II cells becomes moot when you state that the organic mutagens don't seem to be important in rats anyway.

P 10-14, L 33: What is a 'particle relapse process'?

P 10-15, L 11: 'What is a 'lung-free' cell? I didn't know that any cells had lungs.

P 10-16, L 2: Type II cell hyperplasia is a common feature of the lung response of rats. It is either much less, or missing, in other rodents and in primates. The statement is misleading.

P 10-17, para 2: There are lots of problems with the generalizations stated in this paragraph. First, can we presume that the paragraph refers to animals, or are humans included? Second, it's not clear what the author would accept as 'conclusive' or ôdefinitiveö proof. That kind of wording seems hyperbolic. It's hard to imagine what additional data would be required to determine that the tumors in rats occur only at high doses. There are dozens of studies with many different particle types. Third, the recent ILSI workshop concluded that inflammation was a prerequisite for the rat lung tumor response. Of course that workshop occurred after this draft was written. Finally, the information about particles in epithelial cells seems to be tossed in to support a lack of threshold (unless I've missed the point). Of course particles are taken up in epithelial cells. Can we presume that, because of this, the author proposes that there can be no threshold for any particle? Does that make sense?

P 10-18, para 3: Isn't the claim that retention of 14C, and thus organic, is not important in conflict with your premise that humans are at greater risk because of longer clearance times? How do you reconcile the two premises?

P 10-22, para 2: Why is there no mention of the Randerath et al. report on DNA adducts in rats exposed to diesel exhaust and carbon black? That report contains half of what we know about the subject at present.

P 10-22, L 28: It should be made clear that this statement applies only to rats.

P 10-23, L 3: Are there words missing between 'lung' and 'provides'? If not, the sentence doesn't make sense.

P 10-23, L 15: Not a 'greater role', but a greater relative role.

P 10-23, L 20-22: To what information is the author referring when it is stated that DE 'is effective in non-particle-overload conditions'?

CHAPTER 11
GENERAL COMMENTS

This chapter carries forward some of the difficulties in previous chapters, by building on assertions that have questionable basis.

There is no reason that the comparative potency approach is not still useful as a range-

finding estimate of risk; especially when there is no method at present for deriving risk estimates from animal data with confidence. The Agency has had ample opportunity to conduct updated comparative potency estimates based on current mutagenicity (and other) data, using contemporary test materials. This should have been done. Continuing to use comparative potency estimates based on the old Nissan samples is not sensible, in view of the well-known fact that those samples were collected with the engine "de-tuned" to produce more soot than normal.

Continuing to calculate quantitative estimates of human lung cancer risk from low-level environmental exposures from the high-dose rat data is simply not sensible, given our current understanding of those responses. The Agency was advised against that approach at the last review. For some reason, the Agency has decided to directly ignore that advice. The evidence against that approach was adequate then and has been strengthened considerably since then.

Calculating quantitative human risk values from the imaginary tumor response of rats at low doses is not sensible. It might be sensible if the aggregate data from the many studies suggested a response that did not reach statistical significance because of group sizes, but that is not the case. The aggregate data clearly show no response at all in the low-dose regime. Therefore, the agency is only playing 'what if' by using this approach. It is true that such calculations can be done. In the face of our considerable information, however, it is not true that such an exercise is warranted. The logic of this exercise appears to be coupled somehow with the Agency's repeated assertion that the organics play a greater role at low dose levels. If the organics played a role in the rat response, it is true that their role must have been relatively greater at low doses. However, there are lots of data in the low-dose regime, and the aggregate data proved a convincing case against the organics having any apparent effect at all.

The Agency does not advance its case by the above approaches. It is clear that the aggregate epidemiological data, and the results of the most robust of the studies, both make a convincing case for a positive, but small, increase in risk from occupational exposures. It is also clear that our best current hypothesis for this effect is the action of the soot-associated organic compounds. Framing our understanding of the quantitative risk level using the human data and comparative potency comparisons is logical, although we can't estimate risk with a very high level of confidence. In aggregate, the toxicological data support the plausibility of an action of the organics. However, using the rat lung tumor response, real or imaginary, to estimate human risk is not a supportable approach in view of our current understanding.

SPECIFIC COMMENTS

P 11-2, para 2: The negative Mauderly et al. 1996 mouse study is not cited in this chapter, but should be.

P 11-4, L 17-18: While I suppose one can always invoke 'possibility', there is substantial evidence against this assertion.

P 11-5, L 26: It is never mentioned that the Nissan engine was not operated as recommended by the manufacturer, but was 'de-tuned' to produce more soot. Using such samples for risk estimates is not supportable.

P 11-8, L 26: While 1986 is unarguably 'more recent' than 1983, it is hardly 'recent'. Our views of the best approaches for estimating risk have evolved over the past 10 years, yet this chapter does not seem to acknowledge that evolution. The chapter lumps together reports from the beginnings of our exploration of cancer risk and those that are more recent.

P 11-12, L 26: Again, it is asserted that the organic play a 'larger' role at low levels. There is no support for this speculation. There is support for the conclusion that ôoverloadö effects play no role at the lower levels

P 11-13, Table 11-2: These studies were not done using a heavy-duty engine, as the title states.

P 11-15, L 4-7: We know from the substantial data that the risks are not linear in rats, and that the mechanisms causing tumors at high doses in rats most likely do not apply for humans.

P 11-15, L 20-21: We have substantial data showing that the 'particle' effects do not operate at low levels.

P 11-19, L 20-22: How does the Agency propose that exposure from conception increases sensitivity? This assertion is made repeatedly, without citation of any supporting rationale at all.

P 11-20, L 12: What is meant by 'generally'? Have 'significant lung tumor increases' ever been demonstrated at other than 'overloading' doses.

P 11-20, L 27: It should be stated clearly that the 'particle-overload hypothesis' has only been stated for rats.

P 11-21, L 35: EPA has had plenty of time to carry out such a study. The fact that this hasn't been done is a significant deficit in the Agency's approach to the issue over the past 10 years, and particularly over the past 5-8 years when the uselessness of the rat response has become evident.

P 11-23, L 3-4: I disagree that the estimates derived from rats are useful for placing

bounds on human risk. The Agency appropriately uses the estimates from human data to frame their conclusions regarding risk. However, the animal-based estimates are carried through to the final paragraphs and used to frame the range of risks. Based on our current knowledge, the animal-based risks should not be used at all.

CHAPTER 12
GENERAL COMMENTS

This chapter includes two aims: 1) summarizing the characterization of health risks that stem from the preceding chapters; and 2) providing a lay description of the diesel-health issue. These are both good goals, but would be better presented in two separate chapters.

The lay version summary falls short of an accurate portrayal of the issues because of its attempt to simplify language. As presently written, the simplified language is misleading. The task could be accomplished without being misleading, with a more careful choice of wording. No attempt to mislead is implied by these comments, it's just that there are still some technical terms that would be obscure to the lay reader, and word choices in some places actually convey miss-impressions. The section just needs to be edited again with an eye on this problem.

In both sections, more effort should be given to portraying our understanding of risk more accurately by presenting MLEs and distinguishing our 'best' estimates of risk from the upper-bound estimates.

Figure 12 doesn't help a bit. In fact, I became confused by it, even though I felt I had understood the text.

SPECIFIC COMMENTS

P 12-2, L 4: This text seems to imply that 'aggregate' hazard is added on top of the hazard of the individual constituents. Such a 'double whammy' shouldn't be implied unless the authors have some actual information or hypotheses they can provide.

P 12-2, L 17: What kind of cells might be damaged other than 'biological' cells?

P 12-2, L 26: The meaning of this statement is not clear.

P 12-3, L 25-26: The statement that our data 'show' that diesel exposures play a role in the 'development' of allergic disease is a misleading overstatement of our present knowledge.

P 12-3. L 33: Place 'high' in context for the lay reader. I think you mean levels that are 2-3 orders of magnitude above human environmental exposures, but the reader can't tell this.

P 12-5, para 1: You should be careful to state that the information you are relating comes from rats, not all animals.

P 12-5, L 19: It is not clear what you mean by 'short-term basis' The effects are seen over work shifts, but the people are mostly exposed daily over long periods.

P 12-6, L 23: Again, put 'markedly' in perspective. For example, the exposures are about 1000 times environmental levels.

P 12-7, L 1-4: Why use this 1989 Japanese reference when there are U.S. data?

P 12-7, L 21: What 'science policy' is the author referring to? It's regulatory policy, not science policy.

P 12-8, L 7-12: This dissertation on Printex and its surface area doesn't make sense. First, why use the trade name? Second, why state that surface area 'makes up' for its lack of organics? There is no basis in the foregoing chapters for this statement. Third, why not mention the other study (Nikula) that makes up half of what we know about carbon black effects. Is it because the carbon black in that study produced the same effects at a much lower surface area (selected to be like diesel soot in that regard), and that screws up the surface area trade-off hypothesis? Overall, this section just doesn't make sense.

P 12-9, L 3-5: It is true that multiple tumor types were observed in animals. However, multiple tumor types are also observed in humans, and the fact that the tumors in rats differ from those in humans says nothing about whether or not multiple mechanisms are at play. The logic here is unclear.

P 12-9, L 13: Studies of rats that included both males and females consistently found a greater response in females. What is meant by this statement?

P 12-9, L 19-21: What is the point of waving the children's susceptibility flag as a speculation here? What would make them more susceptible? The only data we have on this issue says just the opposite. Is this an obligatory statement?

P 12-10, L 33: Which did you use, 29 or 23? Why state the difference?

P 12-11, L 18-20: This statement is confusing, and its meaning is not clear. You state that all criteria apply 'well', yet go on to state that others may come to a different conclusion. What is the reader supposed to derive from this?

P 12-12, L 16: What does 'nominally' mean - some studies had over 200 subject per group.

P 12-12, L 18: There have been no attempts to produce carcinogenicity in cats or monkeys. Surely you don't think that the investigators seriously thought that their 2-yr studies were a test of carcinogenicity. There were no 'unsuccessful' attempts in these species, because there were no attempts at all.

P 12-14, L 8: What are the 'two components'?

P 12-15, L 24: Stating that there is evidence that a 'majorö hazard is presented by inhalation of diesel exhaust is misleading. One might envision a 'major' hazard from an occupational exposure. Based on present data, it would be a real stretch to imagine a ômajorö hazard from environmental exposures.

P 12-17, L 16-20: The comparison to PM2.5 doesn't have much merit. Diesel soot is included within PM2.5, so you aren't contrasting two different materials, they overlap. Overall, it's not clear that this paragraph adds much.

P 12-21, L 6-15: Why not label this material as a 'tabular summary' as done on P 12-25?

P 12-23, L 6: This statement isn't useful, since there was no response at the lower levels.

P 12-25, L 13-14: It is not clear what 'rationalizing lower limits on risk' means.

P 12-26, L 17-18: That's just the problem. The present document does not discount use of the rat data, and it should (as CASAC has stated previously).

P 12-26, L 31: This statement is confusing. Upper bound risk estimates bound only the upper limits of risk.

P 12-27, L 5: 'Illustrates' is misspelled.

P 12-27, L 9-12: These rat data are from the overload dose regime. This section explicitly intermingles that response with human environmental exposures. It is not clear what useful margin of exposure (MOE) can result.

P 12-27, L 17-19, and P 12-28, Figure 12-1: I don't find that this figure helps at all. I find it confusing, even after some study. A naive reader wouldnt have a chance of getting anything meaningful from it.

P 12-29, L 1-2: Although not all endpoint have been examined, studies have been done in developing rats, and all the data we have indicates that they are less, not more, susceptible.

P 12-29, para 2: First, I though the Cal-EPA draft was marked 'not to be cited or quoted'. Second, where is mention of HEI's assessment document?

P 12-30, L 7-12: Doesn't the recent PM Criteria Document provide a more recent estimate of Pm levels?

P 12-30, L 16: Does ôintegratedö estimate mean a nationwide average, or what?

P 12-30, L 31: Define TEQ.

P 12-30, L 34-25: What does this statement about 'ruling out the possibility of exposures of interest' mean? It isn't clear.

P 12-31, para 2: This paragraph is far too light a treatment of the evolving emissions issue. It is a gross understatement that the data on engine emissions are 'pre-1998'! - I can understand that it's embarrassing to admit how outdated the emissions information in this document actually is. This document requires more information on the nature of emissions from contemporary engines, and the trends that are expected in coming years. There should be mention of fleet turnover times, and projections of emissions into the future.

P 12-32, L 18: It is not clear what 'background means here.

P 12-32, L 30: Can you think of a situation in which exhaust is not 'breathable'? What do you mean here?

P 12-33, L 16: Are you certain that inhalation is the major pathway? I haven't seen a recent estimate, but Cuddihy et al. did an estimate several years ago, and said that more soot would be ingested than inhaled. Is this assertion an assumption, or do you have a methodical estimate you can reference to back it up?

P 12-33, L 19: The statement should be explicit that only a portion of the inhaled particles and gases deposit on lung tissues - in fact it's a minority of the inhaled material.

P 12-33, L 27: I'm not sure what you mean by stating that the symptoms of exposure to diesel exhaust are like the 'onset of a common cold'. The onset of a cold is almost always signaled by a runny nose accompanied by aches and tiredness. Are these the symptoms of 'episodic' exposure to diesel exhaust? Do you mean environmental or occupational exposures? I've been exposed 'episodically' (I think), and I sure haven't had 'cold-like' symptoms.

P 12-33, Last para: I don't understand the context of this paragraph. Remember that

everybody in the U.S. is exposed to diesel exhaust every day

P 12-34, L 25-26: These statements need to be put in context. Are you really concerned about a 'very high one-time' environmental exposure? I can see this section quoted in a lawsuit over permanent injury resulting from the passage of a smoking bus! This whole section needs to be re-thought.

P 12-35, L 1-3: This wording makes it clear that there is a threshold, and that only exposures that are 'too much' increase the likelihood of cancer or noncancer effects. I might agree, but I doubt that's what you intended to state.

P 12-35, L 11: What is a 'test' exposure? This term hasn't been used in any of the animal study sections.

P 12-35, L 24-25: Here again we have the issue of increased susceptibility from exposures in early life. With no evidence given for such an effect, repeating this speculation so many times seems unreasonable.

P 12-36, L 12: Shouldn't 'many' be 'most'? If not, then the value is not useful.

P 12-37, L 22: Here and throughout, it should be made clear that the real risk is expected to be less than the upper-bound estimate. The wording here and elsewhere implies that the risk may be lower, but that's not an accurate view of the estimates. Actual risks are always expected to be less than the upper bound estimate.

P 12-37, L 33-34: Of course a carcinogenic hazard is 'indicated' for ambient PM exposures. What do you think the 6-cities study indicated? Cancer risk was equal to cardiorespiratory risk for long-term mortality (lifespan shortening). Indeed, you ought to be pointing this out clearly , because it is perhaps the strongest supporting evidence for a cancer effect from low-level exposures to mutagenic material in the environment. If it wasn't for that finding, concern for low-level cancer risk would be pure speculation.

P 12-38, para 1: This paragraph doesn't help much. For example, where in the foregoing material was the issue of eutrophication discussed? Is the naive reader supposed to know about this and understand the statement?

Mauderly 5/98

Hopke

General Comments:

I found this document to be lacking in a clear focus and direction. Although we had the list of items from the Office of Mobile Sources as to why they wanted it, I think it suffers from the lack of a clear set of needs specifications to the NCEA personnel writing it as to what it is intended to do and thus, why it has utility. It seems it has suffered from lack of a clear purpose and hence has not been given much attention over the years and certainly very little attention to the modification of the 1995 version before presenting it to CASAC. I suggest that a chapter 1 that clearly lays out what the purpose of the document is and how it is expected to accomplish this goal(s) would provide both the reader and the writers a clearer view of why we are going though this exercise and aim them towards providing the basis for whatever decisions are likely to be based on this assessment.

I can envision several reasons for the document, but none that fit the document as it currently sits. It appears it was started when the assessment of the 1980s technology would have been appropriate for making decisions regarding emissions controls. However, those controls are now set and are being put into operation. Thus, the purposes of this document could either be to assess the impact of diesel emissions on ambient particulate matter concentrations and the toxicity thereof or to look forward to the effect of the reduced emissions that arise from changes in the combustion conditions and the input fuel. In either case, there should be a view to using what we know about diesel emissions and their specific health effects to inform our thinking about ambient $PM_{2.5}$ and vice versa. It is clear that diesel emissions are an important component of $PM_{2.5}$ and yet there are no data to suggest that diesel emissions are significantly different in their toxicity and carcinogenicity from the general ambient aerosol. Thus, we should not be separating the discussion of these two clearly interrelated materials.

Estimating the effects of the existing and planned controls on emissions would seem to be an important albeit difficult task. The changes in emissions has reduced particulate matter with some increase in NOx which would lead to an increased secondary acidic species concentration. The reduction in emitted particle mass may be the result of processes leading to larger numbers of much smaller particles and we are now concerned that the number of ultrafine particles may be playing an important role in PM toxicity. The changes in combustion that increases NOx could also then increase nitrated organic compounds, some of which are known carcinogens. Thus, changes in the emitted organics, both gaseous and sorbed, could substantially change the risk per unit mass of emissions. Some effort to examine this question and at least the acknowledgment that the question exists is important since the controls may be failing to improve public health even if they appear to be lower in concentration. The document clearly requires major revision to give a purpose and then provide the information needed to fulfill that purpose.

Chapter 2
If there have been substantial changes in both engine design and analytical methodology, are any of the results presented relevant to the discussion at hand? The statement at the bottom of page 2-8 lines 35-36) suggests that the rest of the document may be irrelevant to any assessment of new diesel engine emissions and only relevant to the assessment of those older engines that continue in service. It also does not speak to how the older engines might change when they are periodically remanufactured as is common with larger diesel engines. Since can be the particle size, number or nature of the sorbed combustion by-products that are the biologically important emissions components, it appears there is a need for up-to-date sampling and analyses to properly characterize the emissions from current vehicles. There are apparently

no studies of the effects of current diesel emissions on animal models and the epidemiology applies to older engines and in particular those used on trains. Thus, there needs to be a case made as to how similar or different are the emissions from those engines used to generate particles for the inhalation studies. There are published studies of the emissions from new engines. The California diesel document quotes several of them. (Bob or Joe, I have some others that I need to get the references for when I get back home). I do not know if there are studies of the emissions from remanufactured engines, but the question should be asked. If they are qualitatively similar, then old results can be scaled by new emission factors. If there are important qualitative differences, then it needs to be made clear that the old data are not particularly relevant to the further regulation of diesel emissions and that it is critically important to obtain relevant data.

However, diesel vehicles generally have a fairly long functional lifetime. There is some value in understanding the effects of old vehicles in the context of ambient PM. Is there an inventory of vehicles that permits an estimation of how much emissions come from "old" vehicles verses how much from "new" ones?

The nature of chain aggregates also provides the opportunity for more material to absorb since a liquid layer between two spheres will produce a concave meniscus. This is also relevant for chapter 4 since it reduces the volatility of the semivolatile sorbed material (negative Kelvin effect) (Marlow reference). It would also reduce the solubility of these compounds in polar solvents like water and related biological fluids.

Page 2-16 line 7 and 2-17 lines 1-3, how do you know? Reference or speculation?

Page 2-30 lines 5-7, OH measurement and modeling are better now that 1988. This is really pretty far out of date and could be replaced with more modern references particularly the 1994 Atkinson report on arene nitration reactions.

Lin et al. (J. Air Waste Manage. Assoc. 42:1057-1062, 1992) show that one can add tracers to diesel emissions. There are patterns of hydrocarbons that permit assessment of the amounts of gasoline and diesel emissions of modern receptor modeling methods to be applied. See the California diesel document for references to at least 2 published receptor modeling studies and there are others that they missed.

Chapter 4

Tracheobroncial deposition should not be ignored particularly as particle size moves smaller with the newer engine emissions. Although there are some cancers in the peripheral areas of the lung, one should not discount more central locations as a point of focus for lung cancer initiation.

The deposition of particles was further refined by the International Commission for Radiological Protection (ICRP66, 1994) based on considerable new information. The ICRP's new respiratory tract deposition model incorporates more accurate values for the filtration efficiency of the nasal passages (Swift *et al.*, 1992). One important question is the rate of clearance of deposited material. The assumption that the tracheobronchial region is completely cleared by a rapid process has been challenged by a number of investigators beginning with Davies (1980). The main evidence for slow clearance in humans comes from a series of experiments by Stahlhofen and coworkes (Stahlhofen *et al.*, 1980; 1986a,b; 1987a,b; 1990, 1994; Stahlhofen, 1989; Scheuch (1991); Scheuch *et al.*, 1993). The results of these studies are discussed in detail in ICRP66 (1994) in which they conclude that a slow clearance phase cannot be excluded from a complete lung dose model. Thus, calculations based on the ICRP66 model include a fraction of

slow clearance. The presence of a slowly cleared fraction could be important in fully understanding the health effects of deposited airborne particles. The deposition modeling in Appendix C is badly out of date and the whole dosimetry should be repeated with current dosimetry.

Davies, C.N. (1980) An algebraical model for the deposition of aerosols in the human respiratory tract during steady breathing-Addendum. *J. Aerosol Sci.* 11, 213-224.

International Commission on Radiological Protection (ICRP66) (1994) *Human Respiratory Tract Model for Radiological Protection*, ICRP Publication 66, *Annals of the ICRP* 24(1/3) 482 pp.

Scheuch, G. (1991) Die Dispersion, Deposition, und Clearance von Aerosolpartikeln in den menschlkichen Atemwegen (Ph.D. thesis), J.W. Goethe-Universität. Frankfurt am Main, Germany.

Scheuch, G., W. Kreyling, F. Haas, and W. Stahlhofen (1993) Effect of settling velocity on particle recovery from human conducting airways after breath holding. *J. Aerosol Med.* 6(Suppl.) 47.

Stahlhofen, W. (1989) Human lung clearance following bolus inhalation of radioaerosols. In: *Extrapolation of Dosimetric Relationships for Inhaled Particles and Gases*, pp 153-166, Academic Press, Washington, D.C.

Stahlhofen, W., J. Gebhart, and J Heyder (1980) Experimental determination of the regional deposition of aerosol particles in the human respiratory tract. *Am. Ind. Hyg. Assoc. J.* 41:385.

Stahlhofen, W., J. Gebhart, G. Rudolf, and G. Scheuch (1986a) Measurement of lung clearance with pulses of radioactively-labeled aerosols. *J. Aerosol Sci.* 17:333-336

Stahlhofen, W., J. Gebhart, G. Rudolf, G. Scheuch, and K. Philipson (1986b) Clearance from the human airways of particles of different sizes deposited from inhaled aerosol boli. In: *Aerosols: Formation and Reactivity, Second International Aerosol Conference*, West Berlin, Germany, September 22-26, 1986, pp. 192-196, Pergamon Press, Oxford, U.K.

Stahlhofen, W., J. Gebhart, G. Rudolf, and G. Scheuch (1987a) Retention of radiolabeled Fe_2O_3-particles in human lungs. In: *Deposition and Clearance of Aerosols in the Human Respiratory Tract*, Second International Symposium, Salzburg, Austria, September 18-20, 1986, pp 123-128, ed. Hofmann, W.) Facultas Universitätsverlag Ges.m.b.H. Vienna Austria.

Stahlhofen, W., J. Gebhart, G. Rudolf, G. Scheuch, and M.R. Bailey (1986b) Human lung clearance of inhaled radioactively labelled particles in horizontal and vertical position of the inhaling person, *J. Aerosol Sci.* 18:741-744.

Stahlhofen, W., R. Koebrich, G. Rudolf, and G. Scheuch (1990) Short-term and long-term clearance of particles from the upper human respiratory tract as function of particle size. *J. Aerosol Sci.* 21(Suppl. 1):S407-S410.

Stahlhofen, W., G. Scheuch and M.R. Bailey (1994) Measurement of the tracheobronchial clearance of particles after aerosol bolus inhalation. In: *Inhaled Particles VII, Proceedings of an International Symposium on Inhaled Particles Organized by the British Occupational Hygiene Society, 16-22 September 1991* (Eds. Dodgson, J. and McCallum, R.I.) *Ann. Occup. Hyg.* 189.

Swift, D.L., N. Montassier, P.K. Hopke, K. Karpen-Hayes, Y-S. Cheng, Y.F. Su, H.C. Yeh, and J.C. Strong (1992) Inspiratory Deposition of Ultrafine Particles in Human Nasal Replicate Casts, *J. Aerosol Sci.* 23:65-72.

The diesel particle is a chain aggregate and as such undergoes collapse of the fractal pattern when exposed to humidities typical of the respiratory tract (Weingartner *et al.*, Atmospheric Environ. 31:2311-2327, 1997).

Chapter 5
Since there has been extensive studies of the individual effects of CO, SO_2, and NO_x, was there any effort to compare diesel exhaust with comparable exposure to individual gaseous pollutants? Are these gaseous species providing additive or multiplicative risks. Can we see evidence of synergy?

There is evidence that the new engines produce smaller particles. What is the potential implications of the smaller size based on what we know about the effects of ultrafine? We cannot yet say anything definite, but it is critical to point out that the new emissions may be more dangerous even at lower mass emission rates.

Chapter 6
How would the changes in emissions going from old engines to new engines affect the estimation of the RfC. I understand there are no exposure response data to work with, but from an understanding of the differences in the nature of the emissions can anything be said qualitatively about the impact of those changes on non-cancer health effects and hence on the resulting regulatory considerations. What evidence is there that DE is 3 times more toxic than ambient PM2.5? If it isn't, how can we have a NAAQS which is not protective of pubic health with an adequate margin of safety? If it is more hazardous, make the case.

Chapter 10:
What is the take home message from the carbon core section? Since the evidence for effects is only in rats and only under the overload conditions, does the carbon core really have any importance for human cancer risk? If this chapter is to make a mechanistic case for the possibility that the core is important to cancer risk, it never makes the case and thus, does not serve any purpose as written.

For the sorbed organic species, if we know certain compound that are carcinogens are there, are they present in concentrations that would like produce lung cancer. There needs to be order of magnitude estimates that suggest that the presence of these compounds is relevant to estimating risk. Given low concentrations and low deposition, is enough material deposited to provide a significant chance of tumorogenesis? That estimate can be made for B(a)P and some of the nitroarenes and again see if any of this discussion is relevant.

Diesel particles are NOT spheres with a uniform coating of organics.' They are chain aggregates. The physical chemical behavior of chain aggregate aerosols seems to be a total mystery to the report writers. The presence of 5 to 10 nm primary particles in a chain leads to sorption at the interfaces between primary particles. The accumulated layer will accumulate with a negative meniscus leading to a diminished vapor of the material above the particles (Calculations of the Equilibrium Vapor Pressure of Water over Adhering 50--200-nm Spheres, Crouzet, Y. and Marlow, W.H., Aerosol Sci Tech. 22:43, 1995). In an analogous manner, dissolution of sorbed material on these hydrophobic particles will be inhibited and the bioavailability will be diminished as was shown by the early data of Siak et al, 1980 as shown in the presentation of Dr. Vostal.

Chapter 11, page 11-22, line 19 says the animal data are "adequate" to support carcinogenesis. Since only one species (rats) show an effect and only under overload conditions that are in no way relevant to ambient exposures, I do not see how the animal data can be thought of as supportive of carcinogenic particularly given the lack of observed proliferation in the monkey studies. Thus there are no animal data that can reasonably be extrapolated to human exposure conditions that demonstrate that the exhaust is carcinogenic

Chapter 12, Figure 12-1, the x-axis is labelled "dose" when it is clearly "exposure".

This document needs a major effort to properly reflect the nature of current engine emissions, an estimation of what the changes in engine emissions are likely to be and what implications those changes have for public health. Then the document could be used as part of the evaluation of the ongoing mandated changes in diesel engine emissions.

Art Upton

Review of EPA Draft Health Assessment Document for Diesel Emissions

Chapter 10 Metabolism and Mechanism of Action in Diesel Emission-Induced Carcinogenesis

This chapter provides a detailed and appropriately inclusive review of the existing data on the metabolism of diesel exhaust emissions and on the mechanisms that may be implicated in their carcinogenic effects on the lung.

The chapter notes that although the respective roles of the particulate and organic fractions of diesel emissions remain to be established, mechanisms can be envisioned through which either or both fractions may be postulated to exert carcinogenic effects on cells of the respiratory tract

In the case of the particulate fraction, such mechanisms include the release of reactive oxygen species from activated macrophage and leukocytes, resulting in genotoxic and cytotoxic effects on neighboring cells, enhancement of the metabolic activation of procarcinogens, and depression of immunological surveillance.

In the case of the organic fraction, which includes more than 100 carcinogenic or potentially carcinogenic components many of which are mutagenic and have been shown to form DNA adducts in diesel-exposed humans and laboratory animals, genotoxic mechanisms may be postulated to be involved.

In discussing the metabolism and possible carcinogenic mechanisms of diesel emissions, the chapter properly notes the limitations in the available data and the extent to which interpretation of the data must therefore be qualified. Linkage to relevant issues in other chapters needs to be improved, however, especially as concerns the possibility of a threshold in the dose-response relationships.

Chapter 11. Qualitative and Quantitative Evaluation of the Carcinogenicity of Diesel Engine Emissions.

This chapter summarizes the weight of the evidence, presented in preceding chapters of the document, for the carcinogenicity of diesel engine emissions, and it draws on the relevant human and animal dose-response data to arrive at estimates of the carcinogenic potency of diesel emissions for humans. The resulting upper-bound estimates of the risk of human lung cancer attributable to lifelong exposure to diesel exhaust emissions range from 1×10^{-5} /*ug*/m^3 to 200×10^{-5} /*ug*/m^3.

The data and rationale underlying the risk estimates, and the uncertainties inherent in the estimates are presented clearly and documented appropriately; however, the possible existence of a threshold in the dose-response deserves further attention (ie, lower-bound of risk estimates).

Sverre Vedal

GENERAL COMMENTS (charge to CASAC)

1. The available evidence provides no support for a non-threshold hazard due to diesel exhaust exposure.

2. a. The mixing of the epidemiological and animal experimental approaches to deriving upper and lower bounds for risk is admittedly somewhat strange. This reflects doubts about the validity of the occupational epidemiological data and the applicability of these data to the ambient exposure setting. At this time, the large range of risk suggests to me that we are able to only make a qualitative statement about lung cancer risk.

b. There is no basis for selecting a single estimate of cancer risk due to ambient diesel exhaust exposure. The epidemiological data provide the best estimates of risk due to occupational exposure concentrations, but these cannot be extrapolated to the ambient setting.

3. I do not find that the selection of uncertainty factors for the non-cancer outcomes associated with diesel exhaust exposure is scientifically supportable. First, most exposure concentrations associated with adverse effects, even expressed as human equivalent concentrations (HECs), that were used in the animal exposure experiments were several orders of magnitude higher than those present in ambient air and several fold higher (and sometimes over an order of magnitude higher) than those present in the occupational setting. There is no evidence that analogous effects will be present in settings with markedly lower concentrations. Second, whatever precedent may be present for the practice of using a default factor of 10 to derive a reference concentration, it is difficult to follow the logic in this setting. Somehow this factor is intended to account for uncertainty in extrapolating from animals to humans and accounts for the very susceptible subgroups in a population, although only the latter was the justification in this case. In chapter 12, a factor of 3 was used to account for interspecies differences, and a factor of 10 for susceptibles, for a product of 30 and a resultant reference concentration of 5 $\mu g/m^3$ (155/30). While this number is consistent with the recently promulgated $PM_{2.5}$ annual standard of 15 $\mu g/m^3$, this is merely happenstance. The margin of safety for the $PM_{2.5}$ standard was minimal. In short, I do not favor recommending a reference concentration for diesel exhaust based on non-cancer outcomes in addition to the PM standards.

Sverre Vedal

CHAPTER 8

The main issues that are relevant at this point to the epidemiological studies on the association between diesel exhaust and lung cancer are: 1) is there a realistic possibility that the association is still due to residual confounding? 2) is the time course (latency) between exposure and cancer onset observed in the studies plausible? My comments below in general argue that a more thorough discussion of the controversies engendered by the epidemiological findings is needed in the Document.

1. Concern over residual confounding is exacerbated by the relative small size of the estimate of effect. With an effect estimate of only 1.3 (I would therefore take exception with the claim on p. 8-66 that the data on diesel exhaust and lung cancer meet the Hill criterion of a strong effect estimate), one must be concerned that inadequate control for confounding might well result in bias sufficient to produce such an effect estimate.

2. If so, what confounding factor(s) could do this? Obviously, cigarette smoking is the factor of most concern. Many studies, in particular the retrospective cohort studies, did not have the data to allow control for cigarette smoking. However, studies that did have individual data on smoking, and in which some control of smoking was therefore possible, have produced effect estimates comparable in size to those in which control of smoking was not possible. This suggests that smoking was not an important confounder in studies that did not have smoking data, even though smoking was clearly a strong predictor of lung cancer.

3. Confounding due to something other than cigarette smoking is also possible. However, it is not clear what such a factor might be, since it would need to be a reasonably strong risk factor for lung cancer to produce this consistent bias. Concurrent exposure to asbestos might be one possibility, but when it has been possible to account for asbestos exposure, no change in effect estimates has been observed. It seems, then, that no compelling argument can be put forward to support residual confounding as an explanation for the observed effects.

4. Since smoking is such a strong predictor of lung cancer, another possibility is inadequate specification of cigarette smoking that would still allow residual confounding due to smoking. The Garshick case-control study presented several different approaches to specifying cigarette smoking, and there was no meaningful change in the effect estimate resulting from changing the specification of smoking.

5. It could be argued that, apart from incorrect specification of the effect of cigarette smoking in the statistical models, that more general problems with the

statistical models is possible and could result in erroneously observing an effect due to diesel exhaust exposure when none in fact was present. For example, the proportional hazards assumption, required for valid inference based on the proportional hazards model used in the cohort studies, may not be met. Alternatively, misspecification of covariates other than smoking, or inclusion of highly collinear model terms could result in wrong conclusions. Some insurance against all of these potential criticisms is provided by the relative consistency across studies. Although the same mistake could potentially have been made in all of the positive studies with all of the population samples, this seems unlikely. However, more flexible analytic techniques are now available for analyzing cohort data, such as those that address non-linear dose-response. The fact that the effect estimates from the case control studies are also consistent suggests that alternative modelling of the cohort studies is not going to change the findings substantially. A study from Germany presented in abstract form this year (Brueske-Hohlfeld, Am J Respir Crit Care Med, 1998) observed an odds ratio of 1.4, further adding to the consistency.

6. Another interesting feature of the epidemiological data is the marked consistency between studies of the effect estimate size. Although it is still possible that consistent confounding by an unidentified factor could produce such consistent bias, it seems unlikely. It could be argued that this consistency is itself evidence for confounding, since diesel exhaust concentration exposures must have been substantially different across the many studies (although this is not known), which should have resulted in differences in effect estimates based only on crude exposure categories.

7. The review of the epidemiological data in the Health Assessment Document is reasonably complete, with at least one exception. It is not clear to me why "hypothesis-generating" studies were not included in the review (p. 8-1). While such studies are less valuable in isolation when no confirmatory studies have been performed, when a number of subsequent studies have been performed, the logical primacy of "hypothesis-confirming" studies is lost.

8. The issue of adequacy of length of the latency period from the time of onset of diesel exhaust exposure to lung cancer death is potentially a thorny one. In almost all of the studies, the latency period is relatively short. For example, in the Garshick case-control study (1987), cases were defined as lung cancer deaths in 1981-82 with exposure deemed to have started in 1959, although some workers would have had significant diesel exposure before that time. In the Garshick cohort study (1988), only deaths that occurred through 1980 were included. A latency period of slightly over 20 years is short when, for example, one compared the latency period for cigarette smoking. I cannot recall the potential latency period in the Lloyd report on lung cancer in coke oven workers (1971) to determine whether an equally short latency period was present in that setting. It is plausible that an increased risk of lung cancer with such a relatively short

latency period could be observed if what is being detected is the early portion of a latency frequency distribution. A similar finding would also likely occur when the effect of cigarette smoking is examined. Therefore, the relatively short latency period does not necessarily make the observed associations implausible. However, further discussion of this topic is needed.

9. Does the fact that the epidemiological data address the effect of diesel exhaust and its components from "old" diesel engines significantly detract from the value of the epidemiological studies? That is, are they relevant for addressing the potential carcinogenic effects of today's ambient diesel exhaust?

10. Finally, the epidemiological findings and the toxicology findings seem to be somewhat inconsistent. This is a relatively unusual situation where the toxicology is suggesting that diesel exhaust is less toxic (in terms of carcinogenicity) than does the epidemiology. More typically the toxicology suggests carcinogenicity and the epidemiology is either absent or reassuring. Some potential reasons for this anomaly could be residual confounding in the epidemiology studies or inadequacy of the toxicologic models. Some discussion of this is needed. One possibility it that the BaP comparative potency procedure ignores any pathogenic effect due to the particle component, an issue that is discussed in the Document.

In short, I am in agreement with the general conclusion that the epidemiological evidence is "highly suggestive of a causal association between lung cancer and occupational" diesel exhaust exposure. I would like to see a more thorough discussion of the potential for confounding and the latency issue.

Sverre Vedal

CHAPTER 11

Given that epidemiological data are available on the association between lung cancer and diesel exhaust exposure, one would like to be able to make use of primarily these data in evaluating lung cancer risk. Apart from concern that the estimates of effects from these data are still due to confounding bias, the primary limitation in these data is the lack of good exposure data corresponding to the periods of relevant exposure. Nevertheless, realistic estimates of the range of mean exposures have been made, which in turn were used to estimate exposure-response relationships.

The suggested upper bound risk based on an average exposure concentration of 125 $\mu g/m^3$ was 2×10^{-3} per $\mu g/m^3$ This appears to be the upper 95% confidence bound for the effect estimate (see Table 11-1). If so, it is my opinion that this has little meaning. If I understand it correctly, this bound would then be dependent on the precision of the effect estimate from the study utilized. This seems quite arbitrary, and possibly irrelevant, for the purpose of setting bounds for risk For example, one could use the precision based on a meta-analysis and obtain a much different bound. If this bound is not based on the upper 95% confidence limit, but rather based on the actual effect estimate, then I think it has some meaning. Alternatively, an upper bound could be based on some uncertainties in the assumptions (other than the precision of the effect estimate) made to make the risk calculation. Such a bound may also have meaning, and if this is the case, then I might favor it (if I understood what uncertainties were being incorporated in the calculations). The expression of bounds needs to be clarified, as evidenced by my obvious confusion. Chapter 12, the summary, is clearer than this chapter in identifying what the bounds are actually derived from. My overall preference is for an upper bound of 1×10^{-3} per $\mu g/m^3$, which is the maximum likelihood estimate itself for an estimated exposure of 125 $\mu g/m^3$.

Regardless, use of occupational epidemiological data to set bounds to risk, either upper or lower bounds, has a significant limitation in that these data may not be relevant to estimating risk at lower exposure concentrations. That is, even though one can calculate bounds based on the epidemiological data, these may have relevance only to settings experiencing relatively high diesel exhaust concentrations. It is not known whether the exposure-response relationship extends in a linear manner to much lower exposure concentrations. To express risk as lifetime risk due to exposure to 1 $\mu g/m^3$ of diesel particulate matter based on the occupational data is therefore a big leap.

The estimated lower bound risk was not based on the epidemiological data, in which case one might have expected a bound that was lower than the upper bound by a factor of four (based on the estimated upper exposure concentration of 500 $\mu g/m^3$), or an estimate that also incorporated some uncertainties. The bound based on such a calculation naively should not be less by a factor of four, since non-occupational (off work) exposures in the occupational cohorts would be expected to be relatively similar regardless of exposure at work. This would tend to

make total exposure more similar. Nevertheless, the epidemiological data were not used to set the lower bound. This clearly reflects some discomfort in basing the risk estimates entirely on the epidemiological data. Of the alternatives to the epidemiological data to setting a lower bound, I find those based on human data more compelling than those based on animal data. Therefore, I prefer the work using BaP as a dosimeter in which the maximum likelihood estimate of risk was 2.6×10^{-6} per $\mu g/m^3$. It is argued that the main problem with the use of this estimate is that it ignores any contribution of the insoluble carbon particle core of diesel particles to risk. The animal data suggest that the carcinogenic effect of diesel exhaust is due to the particles, or carcinogens bound to the particles. However, this mechanism may only be relevant under overload conditions. But there is evidence of human carcinogenicity of combustion products without requiring a carbon core particle. Therefore I am not clear that the dosimeter approach is irrelevant. In my opinion, given the human data that are available, the assumptions required to apply the animal data result in relatively insecure estimates of risk.

Having said that, my preferred upper bound lung cancer risk is 400-fold greater than my preferred lower bound (1×10^{-3} vs. 2.6×10^{-6} per $\mu g/m^3$), which greatly diminishes the utility of these risk estimates. I therefore do not feel there is much merit to attempting a quantitative risk assessment for diesel exhaust at this time. Extrapolation to ambient concentrations is also problematic.

From: <WHITE@wuchem.wustl.edu>
To: DCFCH01.DCFCHP01(FLAAK-ROBERT)
Date: 5/4/98 17:24
Subject: diesel comments

HEALTH ASSESSMENT DOCUMENT FOR DIESEL EMISSIONS, EPA 600/8-90 057C

Comments by Warren H. White, 5/4/98

OVERALL

This is easily the least accessible document I have yet had to review for CASAC. If it is intended to communicate anything to physical and mathematical scientists like me, it must offer:

a) an introduction that lays out the specific policy questions confronting the Agency, the questions this document is presumably intended to address;
b) a road map outlining the structure of the discussion to follow, explaining to a non-MD how various physiological perspectives relate to each other.

It would have helped me enormously to have read section 12 2.2 (Toxicity Mode of Action) at the beginning rather than the end. By this time I had more or less figured out what AMs do, but here -- finally -- it was spelled right out, in clear and simple language. This is an example of the kind of writing needed earlier in the document.

The "plain-language overview of key information" (section 12 5) is very disappointing. I have a hard time extracting any information of the response to "How does exposure affect human health and how certain are we about these effects?" (P 12-33), for example. "Another aspect of the exposure event is to realize that in a general sense TOTAL CUMULATIVE EXPOSURE AND THE RATE AT WHICH THE EXPOSURE IS RECEIVED IN SOME MANNER INFLUENCES THE NATURE AND/OR THE
EXTENT OF A HARMFUL EFFECT, THIS BEING A TRADITIONAL TOXICOLOGICAL CONCEPT NOT
UNIQUE TO DE." [P 12-34, L 1-4: emphasis in original] Is this anything other than double-talk? What does it mean to say (P 12-37, L 33-34) "Though diesel particulates are associated with a carcinogenic hazard, this is not indicated, per se, for ambient PM exposure."

CHAPTER 2

Post-emission atmospheric transformation is explicitly excluded from consideration in this document, but "primary" emissions are in fact a matter

of measurement convention. Diesel emissions in a hot exhaust pipe differ from diesel emissions diluted ten-fold, and slowly diluted emissions differ from diesel emissions almost instantly diluted a thousand-fold. The descriptions of the inhalation studies in section 7.2 recognise the importance of these methodological details, but the discussion of primary emissions in section 2.3 does not. It is only in section 2.4 that we get a "by-the-way" mention of typical sampling conditions, and an acknowledgment that, for example "more particles in the [ultrafine] may be expected under typical roadway conditions." Discussions of the distinction between carbon core and organic coating are also difficult to interpret without some understanding of sampling temperature and concentration history.

A significant new set of diesel exhaust measurements, specifically designed to support CMB modeling, is available from the Northern Front Range Air Quality Study (NFRAQS). The final report is available at HTTP: //charon.CIRA.colostate.edu.

From: <WHITE@wuchem.wustl.edu>
To: DCFCH01.DCFCHP01(FLAAK-ROBERT),DCWIC01.IN("jmauder...
Date: 5/15/98 19:09
Subject: detailed comments on diesel document

Detailed comments on Diesel Health Assessment, EPA 600/8-90 057C

by Warren H. White

page 2-7; lines 9,10: In aerosol science, "agglomeration" normally refers to aggregation between particles: it is thus inherently not a "gas-to-particle" process

2-8; 1: What are sulfate emissions as a fraction of fuel sulfur?

2-9; 3: The distinction between gaseous and particulate "primary" emissions is operational, a matter of how these emissions are measured. These details are scattered about: e.g., "collected on a filtering medium at a temperature of 52 deg C or less" (2-13), and "a dilution factor of 10 is typical of many dilution tunnels" (2-26). They need to be collected here, and their implications for relevance to ambient particle characteristics discussed.

2-13; 29: As an example of the preceding comment, the "typical" size distribution in Figure 2-1 needs some experimental context: how was it determined? Alternatively, it might be presented as a "conceptual model" of such a distribution.

2-14; 1. The assertion that about 70% of TC is EC in Table 2-4 is supported by the Pierson and Brachaczek data, but the Williams et al. data put the EC fraction at 42% - 64%. And what's the point of "so-called"?

2-58, 6,7: What is the point of putting all this work into a health assessment that is designed to give the Agency no guidance as to whether it should welcome or fear the new technology?

2-59; 7+: This discussion should note the recent NFRAQS study. See HTTP://charon.CIRA.colostate.edu

12-2; 6: The exhaust particles are formed through the AGGREGATION of smaller particles: "condensation" is a gas-to-particle process.

12-2; 7: Change "They" to "The emitted particles".

12-2; 10: Organic compounds (the whole) should be distinguished from organic carbon (a part).

12-2; 22: HD and off-road engines "have the largest U.S. particulate emissions" in what sense? Are we speaking in the aggregate over the inventory category, or on some per-mile or per-engine basis?

12-2; 29: The magnitude of extra hazard is "unknown", it might be discernable if someone looked hard enough.

12-3; 13: Change "shorter and longer" to "shorter to longer".

12-8; 18: Change "rigid" to "strict".

12-26; 11,12: The claim that 1 E-5 "seems to be a floor of all estimates and therefore, establishes the low end for a range of risks" is clearly inconsistent with the earlier (12-22; 22) characterization of 1 E-5 as "The 95% upper bound" of the biomarker estimate, and with the later observation "that as these [sic] all of these risks are upper bound, the true risk is unlikely to be greater and may well be less."

12-32; 4,5: Change to "more than 75% of the material carried by particles smaller than 1 um."

12-33; 4: Note that 200 ug/m3 is over three times the peak 24h health standard for ambient fine particles: should we worry every time we smell this familiar odor? Maybe not, but it's a natural question to ask. The fact that we smell diesel for just a few minutes at a time isn't wholly reassuring, given the speed of olfactory fatigue.

12-33; 19,20: Plain language is not the same as wordiness. This is a good example: Replace "The inhale-exhale pattern of breathing results in some exhalation of the particles and gases;" by "Some of the particles and gases are exhaled;".

12-33; 32+: This whole paragraph seems meaningless blather

12-34; 12,13: The preceding paragraph assumed the reader didn't know the difference between "acute" and "chronic", but here you expect him to appreciate a subtle distinction between "toxic" and "hazardous" And "Taken individually, both" is hardly "plain language".

12-36; 30: If "the true estimate is undefinable", then how "could [it] be much lower"? You mean "undetermined".

12-36; 32,33: "The risk range is thought to bracket the upper limits of possible risk" is hardly plain language. As evident from the discussion of

12-26 above, the very concept of a range of upper bounds invites confusion.

12-37; 6: Change "the probability of cancer" to "the increase in lifetime probability of cancer", and move up in paragraph so reader understands what the numbers at the bottom of 12-36 mean.

12-37; 28,29: Change to "Diesel particles are small: particles of diameter less than 1 um carry more than 75% of the total mass,".

12-37; 33,34: If "diesel particulates are associated with a carcinogenic hazard" and are a ubiquitous component of ambient PM, must we not consider ambient PM a carcinogenic hazard?

Diaz-Sanchez

Chapter 2

Two main problems seem to be evident in this chapter. The first is that it seems out of date. Although it is stated that this chapter has been updated this is not apparent. Secondly, it is stated (page 2-8, line 33) that "detailed chemical characterization of diesel engine emissions was performed in the late 1970s and early 1980s". Since new technology has occurred since that time, it is to be presumed that the composition of the emissions will have changed. This is important even if one does not believe that these chemicals have a role in cancer induction in humans. Several studies have cited the possibility of PAHs and other chemicals to alter immunological effects *in vitro* and *in vivo*. A qualitative or quantitative change in chemical composition would, therefore, be of considerable importance.

Chapter 5

In this chapter and throughout the document, it seems incredible that virtually no mention is made of the extensive work done examining the role of particulates (PM2.5; PM10, etc.) on cancer and non-cancer health effects. For example: epidemiological studies have linked particulate pollution and asthma/bronchitis/respiratory disease. From the studies presented here and others showing a role for carbon black in the inflammatory response and in lesion formation, it would seem that general inflammatory changes, release of inflammatory mediators and lesion formation is mainly due to the particulate nature of diesel exhaust. Immunological changes, however, seem to result from other factors such as PAH although particles may still be needed to deposit them in the right location.. Although it is understandable that the particulate studies do not focus on diesel exhaust and may be due to other factors, it should be noted that DEPM is considered one of the main contributors of urban particulate matter (from 30 to 80%, depending on the study). To ignore the PM studies completely is such an obvious omission that it suggests perhaps a political/policy decision rather than a scientific one.

There is an obvious discrepancy between the animal studies that indicate that diesel exhaust can lead to chronic inflammation, lesions and hypertension and epidemiological studies that show little or no link between diesel exhaust exposure and disease. What are the reasons for this?

a) Have the correct human and epidemiological studies not been done? Do we simply need better, more controlled studies?

b) Are the epidemiological studies not examining the correct endpoint? For example, too few studies seem to focus on asthma, atopy or emphysema, the logical endpoints suggested by the animal studies.

c) Is there no connection between human and animal studies? That is, do studies in rodents not translate into the human condition.

From the studies presented here, it would seem that the answer lies in a) and b). Regardless of the reason, the epidemiological studies are not reliable or consistent enough to be used as measures to calculate an inhalation reference concentration.

Many of the studies regarding asthma/allergic sensitization or induction by diesel exhaust have been overlooked. The knowledge that diesel exhaust particles will act as an adjuvant in mice co-immunized with a bystander protein was shown by Muranaka et al., in the 1970s. Since this time several other groups have confirmed this. *In vitro* and *in vivo* experiments have shown that the PAH associated with diesel exhaust have similar properties (see Suzuki et al; Tsien et al). To present these studies as Òvery recentÓ is somewhat misleading.

Chapter 6

This chapter was obviously written before the uncertainty factor of 3 was reintroduced. Chapter 12 and this chapter must be rewritten to synchronize with one another. An obvious concern is that the studies used to derive the NOAEL are all from studies using rodents, predominantly rats. The work performed on monkeys (Lewis 1986,89) show no effects on monkeys. Is it reasonable to assume that this is due to lifespan. There is an obvious need for more studies in higher mammals to verify this question. However, with the available data, I believe that the Rfc calculation is reasonable with one exception. The use of an uncertainty value of 3 to account for interspecies sensitivity needs to be justified, there is no evidence that humans are more sensitive than rats. In the letter by Dr. Farland it is suggested that allergic hypersensitivity resulting from DEPM exposure occurs in humans but not rats, however, this is not correct since the issue has not been studied in rats Since the 1970Õs experimental studies, exposing different strains of mice to diesel exhaust, have shown that DEP will act as an adjuvant, that is induce allergic antibody formation to bystander allergen. This effect will vary between mouse strains.

In regards to subpopulations with increased susceptibility, it would be predicted that at least for asthma and allergy, allergic/asthmatic individuals would be more at risk. Additionally, it should be noted that in controlled chamber studies on asthmatics only a subpopulation reproducibly showed a decrease in lung function when exposed to secondhand smoke (which includes a high concentration of particulate matter). A similar group of ÒresponsiveÓ individuals may exist in response to diesel exhaust.

Definition of the benchmark concentration is an obvious critical question. How this was chosen needs to be better justified.

Chapter 11

There are two separate issues in this chapter: first, whether the evidence points to a qualitative evaluation of diesel emissions as a potential carcinogen and second whether it is possible to quantify this risk. Overall the diesel assessment performs an adequate job in defining the target organ as the lung. However, estimation of cancer hazards and risk is hampered by the paucity of reliable mechanistic studies. Therefore, despite the large number of published studies, the exact mechanism (if any) between lung damage, carcinogenicity and diesel exhaust exposure is still a matter of

speculation. This becomes important when one needs to choose between a nonthreshold or threshold dose hazard. There seems to be little or no proof that the particle overload effect occurs in humans or indeed in any other species other than rats; the absence of lung cancer in pneumoconiosis afflicted coal miners and particle deposition patterns certainly argues against this. Yet, the human epidemiological data suggest that occupational exposures at concentrations that would in any case occur at concentrations too low for particle overload will increase the risk for lung cancer Although there are inherent problems with these human studies in terms of defining exposure assessment and eliminating other factors, nevertheless there is agreement between nearly all studies that diesel exhaust is associated with an increased risk of lung cancer. Therefore, the qualitative statement that diesel engine emissions are probable human carcinogens is accurate

The question of quantifying this risk is more problematic. It seems clear from carcinogencity studies in the rat using carbon black and other particulate compounds that the particle overload phenomenon is an important toxic mode-of-action in the rat. Evidence for a similar mechanism in other species or at low dose levels in unconvincing. The lack of reproducibility in other species is indeed worrying and begs the question of whether these results are species-specific. The use of this model for establishing low dose human risk estimates is, therefore, suspect. Therefore, it is important to have methods other than just extrapolation from the rat model to determine risk ranges. The use of the model postulated by Chen and Oberdorster is welcome as it has the important advantage of incorporating the carcinogenic potential of both the carbon particle and the associated organics (e.g. PAH, quinones etc.). However, the data used by this model is questionable. Indeed, no one approach seems more valid than another. The use of the human epidemiological data suffers from a range of problems including control of other factors, lack of biomonitoring methods for detecting tissue doses of exhaust, lack of adequate measurement of exact biological effect and an absence of a dose-response effect. The comparative potency method makes significant assumptions that do not necessarily hold true. The use of a biomarker would seem useful, except for the difficulty in obtaining a reliable and unique biomarker for exposure. B(a)P will vary from different diesel emissions and additionally may be found in tobacco smoke and other sources. No one methodology seems superior over the others and any preference would stem primarily from the bias of the reviewer. As a consequence, one can

either reject all these approaches or accept their limitations and compromise with a range of risk estimates. To my mind, the limitations are so great that one should take the first option and not attempt to quantify the cancer risks at all.

5/14/98

To: Robert Flaak, Designated Federal Officer, CASAC

From: Eric Garshick, M.D., M.O.H.
Comments on EPA Health Assessment Document for Diesel Emissions
5/5/98-5/6/98

Chapter 2

This chapter should be updated in order to allow the reader to understand how diesel exhaust has changed over the years. In order to give the reader a sense of typical exposures, exposure levels in different occupational settings might be included and contrasted to estimated environmental levels. Relating occupational exposures would be useful because the epidemiologic studies have been conducted in occupational settings. Recent work by Cass and coworkers on source apportionment might be included (see Health Effects Institute 1995 Report).

Chapter 5

Page 5-1, lines 17-19: There is a study published in abstract form in 1996 that reported the results of bronchial biopsies obtained in normal volunteers following diesel exposure. A influx of polymorphonuclear leukocytes and an upregulation of endothelial adhesion molecules were reported (Salvi SS; Eur Resp J 9(S23): 415S, 1996. If this study has been published subsequently, then it might be useful in understanding the relationship between exposure in humans and subtle inflammatory changes.

Page 5-5, bottom of page: Three cases of asthma are listed here under "Immunologic effects". However, these cases of asthma were not caused by an caused by an immunologic mechanism, but occurred after a short-term exposure to high levels of exhaust (see later discussion of this). It would also be useful to update this chapter on the behavior of diesel particles acting as an adjutant for pollen.

Page 5-79, top page: These comments seem speculative.

Page 5-80, lines 30-36: The rat data do not seem relevant to assess human non-cancer effects since the effects noted occur in conditions of particle. The statement made in lines 3-31 does not seem accurate.

Page 5-82: The short term effects of diesel exhaust exposure can be summarized as an increase in respiratory symptoms characterized by cough, phlegm, and wheeze. In some studies, pulmonary function decrements have been noted across a work shift. Long term effects on pulmonary function and respiratory symptoms are unknown because of only studying active workers and lack of longitudinal data.

Chapter 8

Introduction: Page 8-1, Line 10: In the railroad industry, 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 population was exposed for many more years than actually occurred. Since many epidemiologic studies were done in truck drivers, it would be useful to state that the trucking industry changed to diesel trucks by the 1960's with some companies not using mostly diesel vehicles until the late 1960's. A point can be made in this paragraph is that the date diesel engines were introduced in an occupational setting will influence when an increase in lung cancer might occur if diesel exposure is responsible. Therefore, it is reasonable to exclude studies where the population had a very short duration of exposure and follow-up Since lung cancer has a long latency, it would be worth noting that a weakness of the diesel literature in general is lack of a cohort of workers with a very long duration of follow-up and well-defined exposure (>20 to 30 years)

Page 8-1, Lines 17-18: The results of the studies not specifically discussed due to a variety of limitations might be included in a table. Some of these studies (Siemiatycki et al., 1988, Swanson et al. 1993) have been included in other reviews, such as the 1995 Health Effects Institute (HEI) report and the meta-analysis written by Bhatia et al., 1998. Studies by Guberan et al., 1992 in professional drivers in Geneva and by Gustafsson et al., 1986 could also be included in the chapter. Two additional studies that can be added to the papers discussed are a study of truck drivers in Iceland (Rafnsson and Gunnardottir, 1991) and a study in Swiss professional drivers (Pfluger and Minder, 1994). These studies support the general conclusions of the chapter.

Waller (1981): Page 8-2, Lines 11-12: These lines refer to the study by Waller, 1981. In this study, employed London transport workers aged 45 to 64 at any time between 1950 and 1974 were included in the cohort and followed until death or retirement, whichever occurred first. The sentence in the document suggests that 20,000 employees were followed for 25 years which was not true. Later, on page 8-3, lines 5-7 it is asked whether the ages included refer to the entire period or the mid-point of the 25 years period, or refer to the time period between 1950 and 1964. The author of the article states the study was limited to men aged 45-64 during the period 1950-1974 so these lines can be rewritten to reflect this. The use of 1964 in these sentences should be replaced with 1974.

Page 8-2, Lines 22-23: The major finding of the study is summarized in this one line, and can be written to give additional detail. The engineers in the bus garages had the highest mortality ratio for lung cancer (90%) compared to bus drivers and conductors (75%) and other engineers in a more central repair facility (66%). The bus garage engineers would have had the greatest exposure to diesel exhaust, but motormen and guards without bus-related diesel exposure had a mortality ratio of 87%, similar to the mortality ratio obtained for the bus garage workers.

Howe et al. (1983): Pages 8-3 to 8-5: A limitation of this study not discussed is that only deaths among retired workers were included in the cohort. It is not clear if a worker who developed lung cancer while working would be included in the cohort if disability rather than retirement benefits were requested. Therefore, it is possible that workers with the most diesel exposure were excluded from the study. The details of how the exposure categories were generated were not presented. Nevertheless, an elevated risk of dying of lung cancer in workers probably exposed to diesel exhaust was obtained. Although lines 1 and 2 on page 8-4 indicate that SMR's were calculated in the usual way, an internal comparison among exposure groups was also presented and not indicated here. The potential confounding factor not discussed in this paper or in

this section is exhaust fumes from coal-fired engines. However, death due to lung cancer was not elevated in workers who retired before 1950 who would have had primarily exposure to coal combustion products. The limitations noted are those that can accompany most cohort studies and the effects of these limitations should be discussed. Although it is possible that cause of death may be miscoded, lung cancer tends to be accurately coded in death records. If other cancers are coded as lung cancer, it would diminish the ability of the study to detect an effect of exposure. Although smoking information is not available, the use of an internal comparison group would tend to minimize potential confounding due to differences in smoking among exposure groups. A generic discussion of the effect of smoking and the use of death certificates in the diesel literature might be included in the chapter.

Rushton et al. (1983): Pages 8-5 to 8-6: Comments about this study can be limited to noting there is insufficient information regarding exposure (even based on job title) to draw any conclusions about this study and it seems that the duration of exposure of the cohort was very short. All workers with at least 1 year of work were included, and the duration of "follow-up" was a mean of 5.9 years. It was not clear from reading the paper whether this referred to time of entry into the cohort or time since the first year of work.

Wong et al. (1985): The general discussion about the study seems adequate. The summary can be improved by eliminating such general statements such as in line 13-14: "One has to make do with job histories, which provide limited information on exposure level." The extent that this is true depends on the quality of the job history and how exposure in each job is characterized and should be assessed separately for each study. Although the SMR for lung cancer increased with length of union membership, the greatest limitation in this study is the lack of smoking histories since long term union employees may have been the heaviest smokers when compared to the U.S. general population.

Boffetta and Stellman (1988): Page 8-11, Line 7: The number of males should be 461,981 with known smoking habits, not 46,981 males. However, later in the paragraph it is stated that there were data on 476,648 subjects. These numbers should be reconciled. A strength of this study is the ability to adjust for cigarette smoking, and once this was done, a residual effect of diesel exposure was still noted, with only a modest decrease in relative risk from 1.41 (95%CI 1.19-1.66) to 1.31 (95% CI 1.10-1.54). It would be reasonable to make this point so that estimates of the effect of smoking corrected and crude rates can be compared.

Garshick et al. (1988): Page 8-15, lines 7-9 are duplicates of lines 29-31 on page 8-14. Although the relationship between years of exposure was reported as written in this document, 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 flat to negative depending on modeling methods. These comments have been made previously to EPA regarding these results. In the determination of the relationship between years of exposure starting in 1959, the slope is influenced by the workers with the longest duration of exposure and occur in a limited number of cells where there is under ascertainment of death. 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 have the greatest risk of dying of lung cancer.

Gustavsson et al. (1990): Page 8-17, lines 8-9: The statement that there no dose response relationship is confusing. Later, a dose response relationship is presented based on an exposure index based on job duties and work practices. In line 12, reference is made to a weighted logistic regression analysis; more detail can be given to clarify this since it is not clear what is meant by this statement, or the line can be deleted and the overall results presented. In lines 25-26, the comment is made that cigarette smoking might confound these results. I think it is unlikely because the cases and controls are from the same cohort, and thus the distribution of smoking is not likely to differ between workers exposed and unexposed to diesel exhaust.

Hansen (1993): Page 8-18, lines 26-31: The statement is made that the lack of smoking data and a 36% rural population confound the lung cancer results. However, the authors present an analysis that make this unlikely to be true and should be mentioned. Although the mortality follow-up of this cohort is short, just 10 years between 1970 and 1980, the utility of this study in assessing the effects of using diesel trucks depends on when the Danish trucking industry started using large numbers of diesel trucks. Unfortunately, this is not clearly presented but is suggested to be in the 1950's. This uncertainty should be more clearly stated.

Tables, pages 8-19 to 8-21: Can be modified to more clearly represent the strengths and weaknesses of the studies based on the above comments.

Williams et al. (1977): Pages 8-22 to 8:23: The main weakness of this study is the lack of information linking job title to actual diesel exhaust exposure, and this should be stated.

Hall and Wynder (1984): Page 8-24, lines 31-32: It is stated that since job titles were not validated with work records that recall bias could influence the results. In this study, occupational exposure to diesel exhaust was based on job title rather on self-report of exposure. Based on job title, each subject was classified in very broad exposure categories that would have made a true effect of exposure harder to detect rather than overestimating the effects of exposure. It would be unlikely that recall bias would affect the report of job title in this setting. The study summary can be modified to reflect this.

Damber and Larsson (1987): Page 8-25, line 33. The odds ratio using dead controls for professional drivers with 20 or more years of employment was 1.2 with a 95% CI of 0.9-2.6, not 0.6-2.2. This is smoking adjusted, and is in the range that might be expected given the lack of detail in exposure history. On page 8-26, line 7, the results are summarized as simply saying the study did not find an increased risk of lung cancer in professional drivers and should be modified to reflect these results.

Garshick et al (1987): Page 8-28, lines 12-13: It is written that this case-control study was designed to evaluate the feasibility of conducting a large retrospective cohort study which was not the case. Our group conducted an earlier pilot study to examine the feasibility. Page 8-30, line 3: Instead of post, insert "past".

Hayes et al. (1989): Page 8-33, line 28-29: The sentence ending with the words

...exposures to other lung cancers...should be fixed. In line 31, the effect of job misclassification on the estimates of effect should be discussed, not just that misclassification could occur. The effect would be to make an effect of exposure harder to detect since broad job categories are used.

Steenland et al. (1990): Page 8-35, line 19-20. Although there were no exposure data available for the period of the study, an industrial hygiene survey was done later (Zaebst et al., 1991) that indicated that the mechanics had the highest level of exposure, and the short haul and long haul drivers had similar exposure levels (approximately 25 $\mu g/m^3$). 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 comes from the roadway. These results can be added to the section, and serve to link the air pollution and diesel literature.

Boffetta et al. (1990): Page 8-36, lines 20-23. The comment that no effort was made to verify exposure is difficult to justify here because it was a hospital-based case-control study. Verifying exposure in this setting would have been nearly impossible.

Emmelin et al. (1993): Page 8-38, line 19. change the word "futile" to imprecise.

Bladder Cancer Section: 7 studies are included in this section; studies by Silverman et al. (1983 and 1986), Vineis and Magnani (1985), Risch et al. (1988) are excluded, although the overall conclusions of the chapter will not change. These studies relate work as a truck driver to bladder cancer risk.

Discussion: page 8-59, bottom of the page, discussion about studies in miners. There are 2 studies in miners that have recently become available, one from Australia and one from Germany that was published in a German journal that had an odds ratio of 1.9 (95% CI= 0.6-6.2) in a cohort of 5536 Potash miners. These studies may be available from the Health Effects Institute.

Page 8-62: Discussion about exposure-response in the Garshick et al. (1988) retrospective cohort study: The evidence for dose-response comes from the observation that the younger workers with potentially the longest duration of exposure had the greatest risk of dying of lung cancer. The current line in the document comments that the study found increasing risk with increasing duration of exposure. This statement can be made more precise regarding the findings of the study.

Page 8-63, line 2: The study by Lerchen et al. (1987) was also limited because very few in the cohort reported exposure, not only due to the limitations noted in the paragraph about the study.

Page 8-63, line 8: The study by Boffeta et al. (1990) reported a slightly elevated risk of lung cancer based on self-reported exposure, but not based on occupational classification. The reasons for this include the use of very broad exposure categories that would make it difficult to observe a relationship between exposure and lung cancer, and there were few subjects with exposure. The comments on lines 10-11 "it is interesting to note that he leading risk factor for lung cancer is cigarette smoking" and

"The exposure was not measured" does not fit into the structure of the paragraph and detracts from the discussion.

Relevant Methodologic Issues

Page 8-65: This section discusses relevant methodologic issues. The section on cigarette smoking should include a discussion that although cigarette smoking is a cause of lung cancer, it is only a confounder if there is differential smoking rates among workers exposed and unexposed to diesel exhaust. If a cohort includes workers of similar socioeconomic class, it is unlikely there will be substantial confounding by cigarette smoking.

Other limitations relate to exposure assessment, both in intensity and knowing how long an individual was actually exposed. Given when diesel engines were introduced in the US trucking and railroad industry, there is no study with large numbers of workers with well-defined exposure and mortality ascertainment over 20 to 25 years, although the railroad worker studies come closet to achieving this. 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.

Page 8-69. line 9: There is a comment about a lack of an elevated risk of bladder cancer in cohort studies. In this document, no cohort study of bladder cancer is reviewed in this document. In the HEI document, several cohort studies are noted without an increase in risk noted. A major limitation in the bladder cancer literature is knowing the type of vehicle exhaust fumes the transportation workers studied were exposed to.

Chapter 11

Page 11-1, bottom paragraph: The results of the epidemiologic studies can be summarized in a more concise fashion, with the limitations listed and their impact on the estimates of risk rather than just stating there are "major" limitations in line 33). A summary might include the points that the literature is unlikely to be confounded by cigarette smoke; the effect of using job title would be to underestimate the effect of exposure. Measurements of actual exposure are lacking, as does the study of a cohort with years of well-defined exposure and follow-up, given the long latency typically observed in lung cancer.

1986 Guidelines, page 11-1: I agree with the wording of how carcinogenicity is described given the constraints of these guidelines.

1996 Guidelines, page 11-3: I agree with the qualitative statement made. I think that confounding factors are not the major concern in the diesel literature, but relate to the assessment of exposure duration and intensity, as well as the lack of studies with long term follow-up of exposed workers. Given the time period of the introduction of diesel engines in the railroad and trucking industries (late 1950's-1960's) , until recently it has not been possible to design such studies.

Page 11-4, lines 2-3: The statement is made that the results of inhalation experiments

in mice were equivocal, but in the previous section (page 11-2, lines 10-11) positive results in two experiments in mice are noted. This should be clarified.

Page 11-10, lines 16: 1945 should read 1959.

Page 11-10, lines 18-21: As noted earlier, the relationship between years of exposure starting in 1959 and lung cancer mortality in the cohort study was influenced by additional analysis that adjusted for age at death rather than age at entry into the cohort, and by the missing deaths after 1976. The relationship might also be influenced by considering exposure before 1959. In the analysis presented in the paper, exposure pre-1959 was not considered.

Page 11-10, line 27: The comment is made that the differences between the results obtained by Dr. Dawson and Dr. Crump cannot yet be explained. A summary might indicate that the differences are related to how background exposure is used in the modeling, the use of different markers of exposure in some models, and how age and calendar year are handled in the regression results.

Page 11-10, bottom of page: The mean values obtained by Woskie et al. ranged from roughly 50 μg/m3 to 100 μg/m3 for the train riders and 120 μg/m3 to 160 μg/m3 for the shop workers as presented in the second of the exposure papers. Exposure varied based on the period of exposure since the earlier engines historically weren't as clean as later engines. The equipment on the four smaller railroads that were sampled was weighted towards early equipment (1950's) rather than later generation diesel engines (built in the 1960's and 1970's). We estimate that the actual historic values of exposure were likely 2 to 4 times the values we measured, and there is some indication the historic values could have been 10 times as great. Part of the uncertainty of performing a risk assessment due to estimating these historical levels and applying them in any model selected. The relationship between personal exposure to diesel exhaust and lung cancer occurrence in the railroad worker database is therefore uncertain.

The railroads gradually replaced steam locomotives with diesel locomotives throughout the 1950's. The date that this happened for each worker was not available, although industry average data are known. Some workers may have used diesel equipment starting in the late 1940's and early 1950's, and others 10 years later. Due to this uncertainty, the regression results using years of exposure was based on exposure starting in 1959 because 95% of the locomotives in service were diesel by 1959. Therefore, the use of the regression results from the case-control study doesn't take into account pre-1959 exposure that was more intense. The regression coefficient overestimates the risk per year.

Since we know which railroad each worker last worked on and railroad employment was very stable, it is possible to refine estimates of pre-1959 exposure by using information from railroad rosters to estimate the conversion date from steam to diesel for each worker, and estimate the conversion from first to second generation engines. In my opinion, analyses could be done that consider the uncertainty in past exposures. These analyses could be done for both the case-control and retrospective cohort study, and would give insight into the uncertainties in using these data for risk assessment rather than using one slope based on the case-control study in this document. In the cohort study, this uncertainty would be reduced by obtaining additional information on deaths after 1976 given the short duration of follow-up at present time (1959-1976). In

my opinion, analysis of the current retrospective cohort database indicates that the exposure-response relationship cannot be described by a single slope.

If we use these data to estimate the risk per μg of inhaling ambient diesel over a lifetime it also indicates that we are confident that the type of exhaust generated is similar to more recent exposure. Additional research is needed in this area.These data seem to be more relevant to estimating risk for workers with higher level occupational exposures. Use of these data are also limited by not knowing if we are using the right marker of exposure since we do not know the biologic mechanism of how diesel exposure results in lung cancer in humans. These points need to be made qualifying the results of a quantitative risk assessment.

If a quantitative risk assessment is needed to regulate diesel exhaust, particularly given new technology, it should be acknowledged that the best information would be obtained from a study that better able to link personal exposure to health outcome, and is designed to determine a dose-response relationship. Given the uncertainties in the risk assessment regarding extrapolation to low dose exposure at this time, I am concerned that any number calculated will be taken out of context.

Page 11-11, line 5: It is not clear what is meant by maximum likelihood estimates of mortality. In looking at the calculations done by Dr. McClellan in the original reference, it is not clear to me how the values used in the current EPA report based on the human data are derived and these calculations should be shown.

Page 11-11: Use of the animal bioassay data. My opinion is that the animal bioassay data should not be used to estimate human risk, particularly at low exposures.

Page 11-22: The conclusion that diesel is a probable human carcinogen is valid.

Chapter 12

This chapter is largely based on previous chapters, and its content reflects the knowledge and uncertainties of the past chapters. In general, it is poorly written and contains material that is speculative regarding mechanisms and health outcomes. It needs to be rewritten once the other chapters are rewritten.

Page 12-2, lines 23-25: The relationship between more recent and past exposure is mentioned. There is some information available regarding this rather than simply saying "There is no single answer to this question". The type of missing information needed can then be described.

Page 12-3, lines 26-27: This section suggests that hypersensitivity to diesel exhaust occurs and is based on an immunologic reaction. At this time, I don't think this conclusion is justified. There were 3 cases of asthma that were noted following high level exposure. The mechanism of this is likely not to be immunologic since the case reports share similarities with patients who develop asthma following a single massive exposure to an irritant gas, fume, vapor or smoke. The authors of the paper note that the mechanism needs further clarification and speculated on the role of allergy. On line 27 the phrase "other ambient contaminants" occurs. It is not clear what this refers to.

Page 12-5: The sentence "Because of the key role alveoli play in the exchange of

gases, these changes may inhibit the efficiency of pulmonary function" is written referring to episodes of pulmonary edema in animals exposed to high levels of diesel exhaust acutely. The terminology "pulmonary function" usually refers to pulmonary function test results. It would be more precise that this could lead to hypoxia.

Page 12-5:, lines 19-29: The language describing the health effects here is written poorly, such as the sentence "Several studies of workers occupationally exposed to diesel exhaust on a short-term basis have monitored pulmonary function at the beginning and end of work shifts to see if this marker of respiratory distress have been impaired by exposures". This should be rewritten.

Page 12-5, bottom: The findings of a chronic respiratory impairment due to diesel exposure are overstated here, as is the comment that there is immunologic based lung disease at the top of page 12-6. The literature of long term pulmonary function changes in humans is quite limited and inconsistent, and it is not clear that reported changes in pulmonary function were due to exposure in the studies.

Page 12-6: Animal results are noted here regarding non-cancer health effects. It is not clear that this is relevant to human disease.

Page 12-7, bottom: The statements made here suggest that diesel exhaust can cause emphysema. Has this been supported by experimental data? The sequence of events noted in this section seems to apply only to animals exposed under particle overload conditions.

Page 12-9, line 16-17: A comment is made about "toxicological wisdom". This should be made more precise.

Page 12-10, line 17: A comments about a 20% to 70% elevation in risk is made based on the exposure-response relationship from the cohort study. This sentence is based on the relationship with years of exposure, and should be deleted.

Page 12-11: The language selected to describe the epidemiologic studies is poorly chosen. This section should mention also that studies with workers exposed for a longer duration and with more years of follow-up are needed.

Page 12-19, line 32-33: The case control study was not nested within the retrospective cohort.

Page 12-20, line 30: The comment is made that the use of 500 µg/m3 has "no particular support, though it can't be ruled out"...I believe more informative statements can be made about historical exposures in the railroad industry.

Page 12-21: As noted earlier, it is not clear how these calculations are related to the original calculations presented. I also question whether 500 µg/m3 is likely to be in the overload range (lines 23-24).

Page 12-25: As noted earlier, the rat data do not seem adequate for human risk assessment.

Page 12-27: I question whether much of the paragraph on susceptible subgroups is

speculative, particularly at ambient diesel concentrations. This section implies that ambient diesel can worsen pulmonary fibrosis.

Page 12-37: I am very concerned about quoting cancer risks of 1/100 due to ambient diesel. It is very likely that the risk is much less. Is it necessary to use quantitative methods to assess health risk? Is a qualitative description sufficient?

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May 11, 1998

Mr. Robert Flaak
Designated Federal Officer
Clean Air Scientific Advisory Committee
U.S. Environmental Protection Agency
Washington, DC 20460

Dear Mr. Flaak:

Enclosed are my written review comments on the "Health Assessment Document for Diesel Emissions" (February 1998 SAB Review Draft). These comments are intended to complement the oral comments I made at the meeting of the Diesel Review Panel on May 5–6, 1998.

As I noted at the meeting, the present document does not represent an update review and synthesis of the available data on diesel emissions and, thus, is not an adequate document for regulatory decision-making. Although some portions of the document are improved over the 1995 draft, the present draft is highly uneven in its coverage of the published literature. Moreover, the document is seriously flawed in its interpretation of the extensive body of data available on lung cancer in rats chronically exposed to high levels of diesel exhaust. The mechanistic data now available indicates these findings are not relevant for assessing human lung cancer risks from ambient environmental exposures. In addition, contrary to statements in the report there is no compelling evidence that the organic fraction of inhaled diesel exhaust particles causes lung cancer in rats. And finally, the document overstates the potential utility of the existing epidemiological data for quantitatively estimating human lung cancer risks from ambient environmental exposures to diesel exhaust.

Several portions of the document would have benefited from cross-referencing the recently completed criteria document and staff paper on airborne particulate matter. This is especially the case regarding derivation of an RfC. The report did not present compelling evidence to support an RfC 5 $\mu g/m^3$ as opposed to adapting a value of 15 $\mu g/m^3$ based on the recently promulgated $PM_{2.5}$ annual standard of 15 $\mu g/m^3$.

I urge the Agency to proceed with revision and updating of the document at an early date. Delays in updating the document will result in some sections which are

now nearly current becoming out-moded. Alternatively, the updating and revisions could be done concurrently with preparation of the next criteria document for airborne particulate matter.

Sincerely,

Roger O. McClellan

Roger O. McClellan, D.V.M.

ROM/sl

Enclosure: Review Comments

cc: Dr. J.L. Mauderly, Chair
Clean Air Scientific Advisory Committee

Chapter 2. Diesel Emission, Transport, and Transformation

The present chapter is seriously deficient in two areas. First, the chapter does not clearly describe in quantitative or semi-quantitative terms, the substantial changes in diesel engine technology, and fuel quality that have occurred over the past two decades. Second, the chapter does not adequately describe the most recent research findings on the influence of exhaust control technologies or emissions.

Chapter 4. Dosimetric Factors

This chapter reviews the relevant literature on the disposition of inhaled diesel particulate material (DPM) as it existed in 1994. The chapter is deficient in not reviewing substantial literature published since 1994. Some of the newer literature and analyses were included in the most recent Particulate Matter Criteria document compiled by EPA.

A major deficiency of the chapter is the failure to integrate and synthesize the information presented. Thus, the chapter in its present form is an exposition on dosimetric factors. What is needed is an integrative treatise on the "disposition of inhaled diesel exhaust." The chapter appropriately concentrates on the fraction of DPM deposited in the lower respiratory tract. The chapter's coverage of the key concept of "particle overload" in the rat should be expanded (See McClellan 1996). The coverage of this issue could be enhanced by including two figures based on the work of Wolff et al. (1987) (attached). The text should more clearly describe the inter-relationship between particle burden, inflammation and impaired clearance and how each builds on the other.

The chapter could be improved by providing some quantitative estimates of DPM deposition and retention in the human respiratory tract especially the tracheobronchial and alveolar regions. Such information would aid the reader in appreciating the small quantities of DPM including particle associated organics predicted to be deposited under the highest levels of plausible human exposure.

Quantitative estimates can be developed using the information presented in Table 4.1 and the paper by Xu and Yu (1987) that is the source of Table 4.1. Table 1 from Xu and Yu (1987) is attached and should probably be included in the chapter. As an aside, I believe this paper was included in a report by C.P. Yu to the Health Effects

Institute. The Health Effects Institutes report includes a critique of the Xu and Yu work which should be considered by the author(s) of the chapter in citing Xu and Yu.

From the paper of Xu and Yu the following may be calculated for an individual continuously exposed to diesel exhaust particles at 1 $\mu g/m^3$ with 20% organic content and methylanthracene (as an example) as 10^{-3} of the total organics and 1,6-dinitropyrene (as an example) present as 10^{-6} of the organic fraction.

	Annual Deposition in Lung
Total Diesel Particulate Matter	420 μg
Total organics	84 μg
Methylanthracene	84×10^{-3} μg
1,6-dinitropyrene	84×10^{-6} μg

These values for continuous exposure to 1 μg of DPM/m^3 can readily be scaled to higher or lower air concentrations. Although the precise estimates may be open to criticism in may opinion they are accurate to within a factor of 2–3.

Information such as discussed above is useful in understanding the apparent contradiction between diesel exhaust particles containing known or suspected carcinogens yet their being no clear carcinogenic signal in humans and no clear signal that the organics are causing lung cancer in rodents. At high concentrations of even a few hundred μg of DPM/m^3 the amount of carcinogenic material delivered to the lung is apparently well within the capacity of the lung to detoxify the organic compounds. The delivery of huge quantities of these chemicals to isolated cells in in vitro studies on the other hand results in clear signals for mutagenicity.

A recent review paper on pulmonary retention and clearance of inhaled biopersistent aerosol particles by Stöber and McClellan (1997) will be useful to the author in updating the chapter. A recent review by McClellan (1997) on the use of

mechanistic data in assessing human risks from exposure to particles provides guidance for reconciling the in vitro and in vivo findings.

References

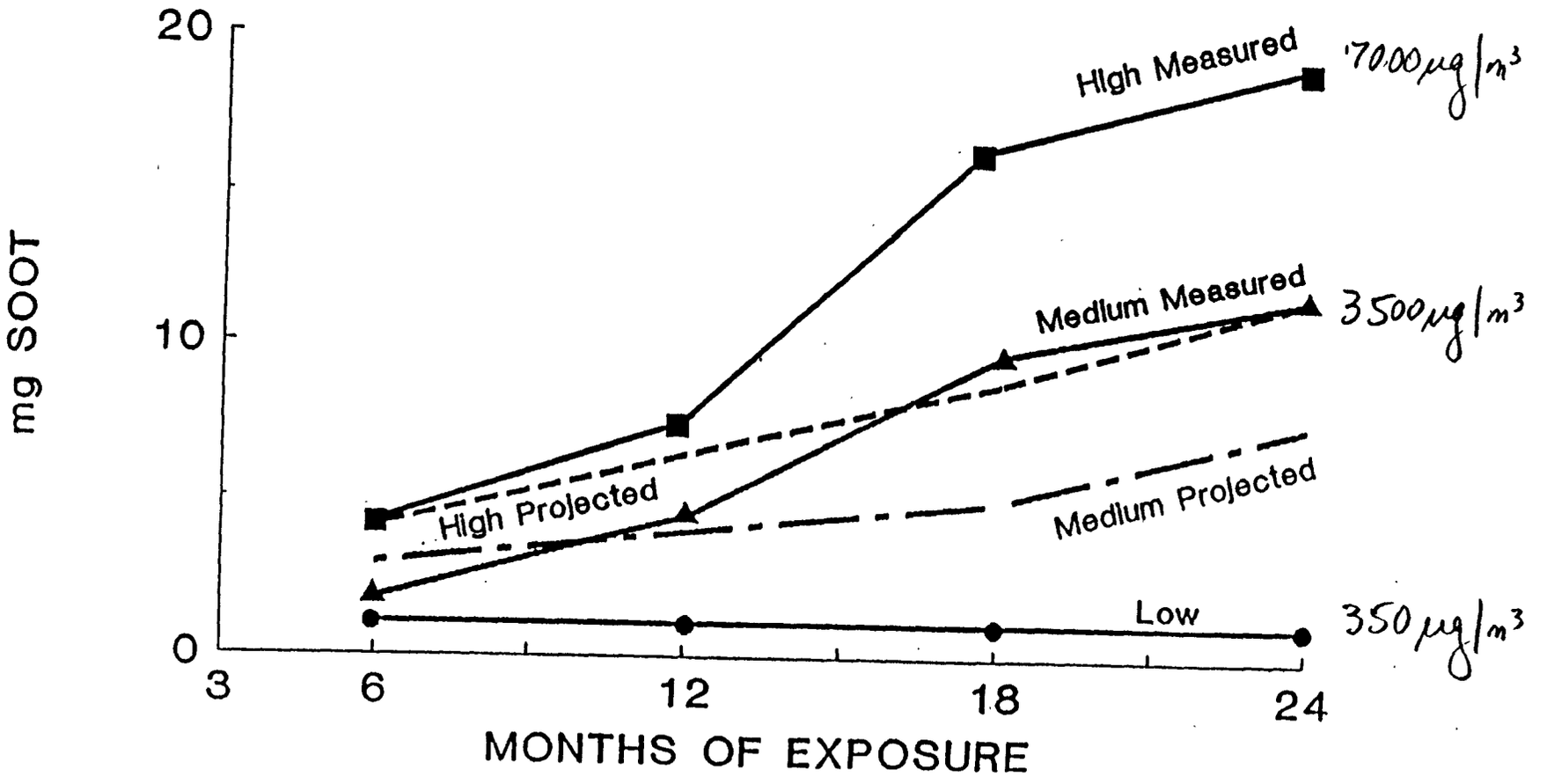
McClellan, R.O. (1997). Use of mechanistic data in assessing human risks from exposure to particles. Environmental Health Perspectives 105 (Supplement 5):1363–1372.

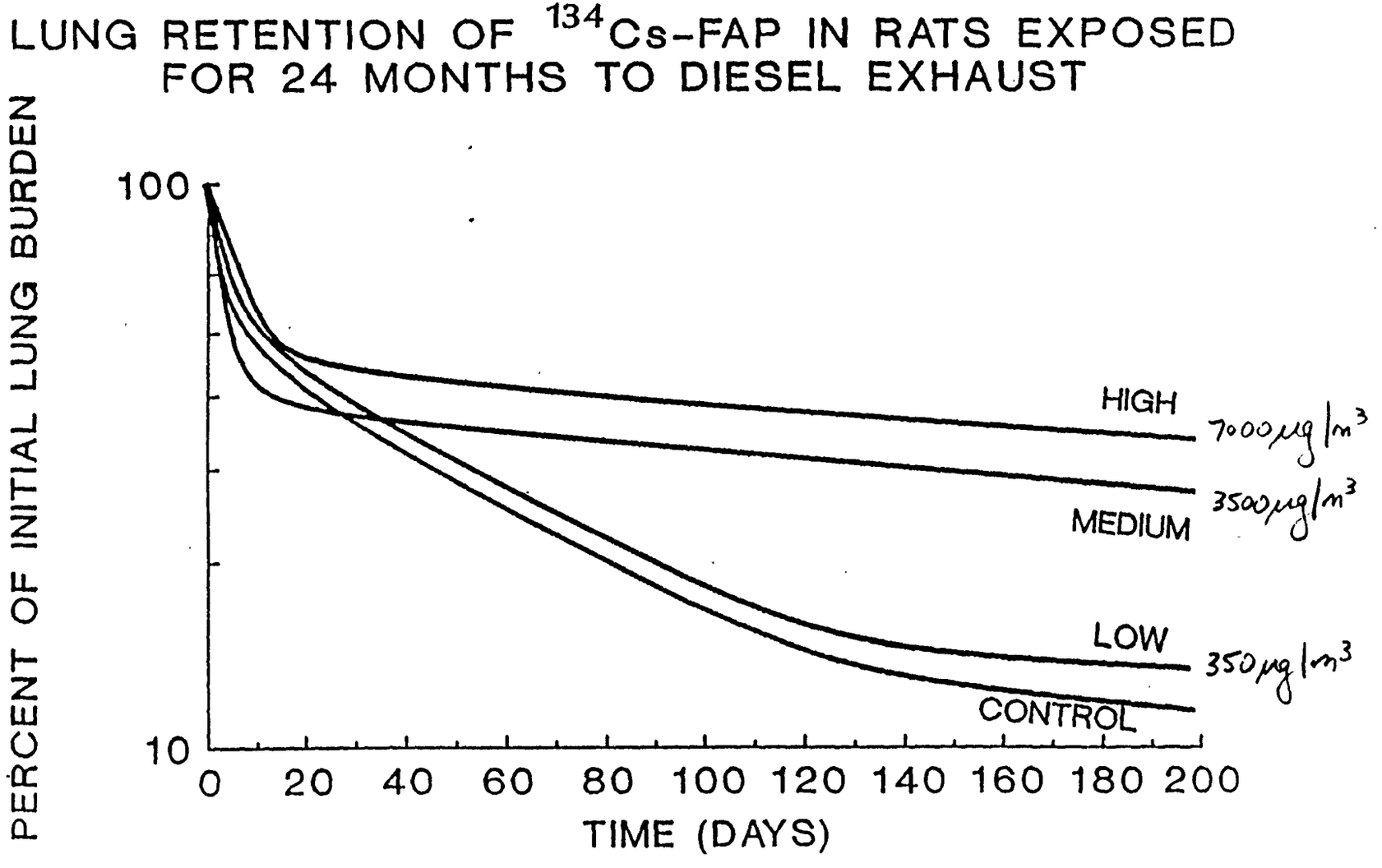
McClellan, R.O. (1996). Lung cancer in rats from prolonged exposure to high concentrations of particles: implications for human risk assessment. Inhalation Toxicology 8 (Supplement):193–226.

Stöber, W. and McClellan, R. O. (1997). Pulmonary retention and clearance of inhaled biopersistent aerosol particles: data-reducing interpolation models and models of physiologically based system. Critical Reviews in Toxicology 27(6):539–598.

Xu, G. B. and Yu, C. P. (1987). Deposition of diesel exhaust particles in mammalian lungs. A comparison between rodents and man. Aerosol Science and Technology 7:117–123.

LUNG BURDEN OF SOOT IN RATS CHRONICALLY EXPOSED TO DIESEL EXHAUST




LUNG RETENTION OF ^{134}Cs-FAP IN RATS EXPOSED FOR 24 MONTHS TO DIESEL EXHAUST
PERCENT OF INITIAL LUNG BURDEN
100
10
0
20
40
60
80
100
120
140
160
180
200
TIME (DAYS)
HIGH
7000 µg/m³
MEDIUM
3500 µg/m³
LOW
350 µg/m³
CONTROL

Roger O. McClellan
May 4, 1998

Chapter 7. Carcinogenicity

This chapter is a comprehensive compilation of all the studies conducted in laboratory animals to evaluate the carcinogenicity of exposure to diesel exhaust and organic extracts of particles. However, the author has not adequately integrated and interpreted the data. This deficiency is apparent early in the chapter as the section on inhalation studies in rats starts immediately with a detailed description of a single study. The same flawed approach is true of other sections. An introductory paragraph could be used to good advantage to alert the reader to what will follow.

The author has apparently not critically read all of the referenced studies. For example, the author appropriately notes on page 7-40, lines 27–28 that most rat studies indicate a trend of increasing "lung" tumor incidence at exposures exceeding 1×10^4 mg • hr/m^3. This is followed by the erroneous statement — "A similar comparison could not be adequately made for mice, because experimental designs were not comparable." The author is reminded that the rat study of Mauderly et al. (1987) showing the trend of increased lung tumor incidence at high exposure concentrations was conducted concurrently with the negative mouse study reported by Mauderly et al. (1996). Why does the author not view these two designs as comparable, indeed identical. The reason a similar trend is not seen for mice is that the studies are generally negative.

A significant deficiency in the chapter is the failure to note the substantial changes in diesel engine technology and fuel quality over the past two decades. The result has been substantially reduced diesel particulate matter emissions. The data available on diesel exhaust carcinogenicity was obtained with engines that fall far short of today's technology. For example, the Lovelace studies with rats and mice were conducted using a 1980 General Motors V-8 diesel engine with the exhaust for

the high level animals diluted about 1 to 10 with clean air to achieve a concentration for the high level animals of 7 mg/m^3. I suspect if the study were repeated today it would be necessary to use undiluted exhaust to get 7 mg/m^3 and O_2 would have to be added to sustain the animals.

The chapter is also deficient in not more clearly pointing out that most of the carcinogenicity data was obtained in exhaust from light duty vehicles with only limited data available for exhaust from heavy duty engines. There is a shortage of information available on DPM from locomotives or boats/ships powered by diesel engines.

The summary is excessively long and is somewhat misleading. The last two paragraphs definitely need to be rewritten. The author needs to make it clear that positive lung tumor findings in rats are high exposure concentration dependent and are very likely species dependent. It should also be emphasized that the data on carcinogenicity of the organic fraction of DPM is based on high dose skin painting studies. There is no evidence for the organic fraction contributing to lung cancer in the rodents.

The statement (page 7-44, lines 17–18) that the relative importance of the absorbed organics remains to be elucidated is misleading. The present evidence is compelling for the adsorbed organics having no role in the pathogenesis if the lung tumors observed in the rats.

Roger O. McClellan
May 4, 1998

Chapter 9. Mutagenicity

The body of this chapter is a well-written review of the substantial amount of data available on the mutagenicity of DPM in bacteria mammalian cells and intact rodents.

However, the chapter is deficient in not including the results reported by Driscoll, Oberdörster and colleagues (1996) on mutations observed in lung cells of rats exposed to high concentrations of carbon-black. Admittedly, carbon black is not DPM; however, carbonaceous material is the major constituent of DPM. Because carbon black used by Driscoll and Oberdörster was free of any significant quantity of PAHs, it is generally accepted that the mutations in the carbon black-exposed rats arise as a result of damage from oxygen radicals produced by chronic particle-induced inflammation. There is strong circumstantial evidence linking the high lung binders of particles with chronic inflammation with increased lung cell mutations with increased lung cancer in rats exposed to DPM, carbon black, and several other kinds of particulate matter (PM). This effect appears to be rat specific and not relevant for assessing human cancer results of PM.

A second deficiency in this chapter is the failure to note that the vast majority of the mutagenicity data was obtained on DPM (and extracts) collected from engines manufactured a decade or more ago. The advances in engine technology and fuel quality over the last two decades has been substantial. Particulate emissions have been substantially reduced. It would be surprising if the chemical composition of the organic fraction had not changed, thus influencing mutagenicity. The old data may be qualitatively relevant to the new engines but very likely do not have quantitative relevance.

The first two paragraphs of the summary are appropriate. The third paragraph overstates the uncertainty in DPM as being of concern for producing veritable genetic

risks. In this reviewer's professional opinion, chronic exposure to DPM at the highest plausible levels of human exposure does not pose any veritable genetic risk.

The fourth paragraph of the summary borders on the incoherent and needs to be rewritten.

Reference

Driscoll, K.D., Carter, J.M., Howard, B.W., Hassenbein, D.G., Pepelko, W., Baggs, R.B., and Oberdörster, G. (1996). Pulmonary Inflammatory, Chemokine, and Mutagenic Responses in Rats after Subchronic Inhalation of Carbon Black. Toxicology and Applied Pharmacology 136:372–380.

Roger O. McClellan
May 4, 1998

Chapter 12. Health Risk Characterization for Diesel Engine Emissions

This chapter fails to meet the stated objective of integrating and summarizing the key findings about the health hazards and risk potential for humans exposed to ambient levels of diesel exhaust. The failure to meet the stated objectives relates to deficiencies in the earlier chapters. Many of these chapters do not contain information published since 1994 and, thus, provide an incomplete basis for developing a summary chapter. In addition, many of the chapters while prefacing extensive compilations of published work fail to provide a crisp summary of key conclusions. This absence of critical summarization in individual chapters makes it difficult to prepare an overall integrated summary chapter.

A critical deficiency in Chapter 12 is the failure to adequately convey information on the marked changes in diesel engine technology and fuel quality that have occurred over the last two decades. As noted earlier in my comments, it is important to recognize that most of the data available on health effects of diesel exhaust in laboratory animals were derived using diesel exhaust from engines that are now out-moded and the fuels are of inferior quality as compared to the fuels used today. It is crucial that these differences be considered when risks are being estimated for current technologies.

It would also be helpful if the chapter were to more clearly distinguish between information obtained with light duty diesel engines versus heavy duty engines.

The chapter fails in many areas to place observations within a quantitative framework. For example, the descriptions of acute, short-term and chronic exposure on pages 12-3 to 12-7 make no reference to the exposure concentrations that elicit the various endpoints observed. Likewise, the description of "toxicity mode of action" on pages 12-7 to 12-9 is presented without adequate discussion of how the exposure

level influences the "mode of action." See the papers by McClellan (1996) and McClellan (1997) on the importance of considering exposure level specific effects.

Finally, on page 12-12, quantitative data are presented with a concluding statement that responses were not detected in rats or mice at lower exposure concentrations of 350-2,200 $\mu g/m^3$ in contrast to the lung tumor responses observed in rats exposed to higher concentrations. The author then proceeds to hypothesize that positive results would have been observed at low concentrations if this study had used more animals. What the authors should have noted is that in a pooled analysis by Valberg (1998) he determined that 1212 rats had been exposed to average lifetime diesel exhaust concentrations from 50 to 550 $\mu g/m^3$ without an excess lung tumor risk having been observed compared to 1135 controls. These exposure concentrations did not elicit an overload effect (inflammation, impaired clearance, mutations and lung tumors) so the potential existed for tumors to be observed due to the diesel exhaust particle organic constituents. An excess incidence was not observed.

This absence of an effect is totally compatible with the low quantities of individual organic compounds that are actually inhaled and this apparent low potency for eliciting mutagenic and carcinogenic responses when detoxification mechanisms are not overloaded.

The section 12.2.4 (Weight of Evidence Summary) overstates the current status of knowledge on the human carcinogenic risks of diesel exhaust. I agree with the conclusion that the human epidemiological evidence is "limited." I strongly disagree with characterization of the rodent data or "sufficient evidence" absent qualification as to the requirement for high level chronic diesel exposures being required to elicit "positive" effects in rats.

I would characterize our present knowledge from epidemiological, laboratory animal and mechanistic studies as supporting a classification of diesel exhaust as a

"possible" to "probable" human carcinogen with likely low potency at plausible environmental levels of exposure to diesel exhaust. The data are not suitable for deriving quantitative exposure lung tumor response relationships.

I disagree with the derivation of an RfC value of 5 μg diesel particulate matter per m^3. The use of an uncertainty factor of 10 and an RFC of 15 $\mu g/m^3$ would be appropriate. This value is compatible with the Agency's recent promulgation of an Annual $PM_{2.5}$ standard of 15 $\mu g/m^3$. In my opinion, the $PM_{2.5}$ annual standard arrived at through "expert judgment" and "policy calls" should take precedent over the use of a process that uses some arbitrarily selected uncertainty factor.

The chapter then proceeds to relate some quantitative estimates of this risk potency of diesel particulate matter using four approaches: epidemiological studies, Benzo(a)pyrene as a biomarker, animal studies, and a comparative potency approach. The epidimiologic approach builds on a "back of the envelope" approach I advanced a decade ago. Much additional information has been developed over the last decade causing me to reassess my own earlier statements as well as earlier statements of other individuals. In my opinion today, none of the approaches are fully satisfactory for providing quantitative estimates of human lung cancer risk. They all have serious limitations which should be more clearly articulated in this chapter.

The epidemiological data are not sufficiently rodust for developing quantitative estimates of risk. Moreover, our knowledge of the exposures clearly precludes development of quantitative estimation of potency for lung cancer induction by diesel particulate matter.

The benzo(a)pyrene biomarker approach is flawed because it does not appear that benzo(a)pyrene has any role in diesel particulate matter causing lung cancer. The animal studies do not provide a basis for estimating human lung cancer risk

because the mechanisms by which diesel particulate matter causes lung tumors in rats is not relevant for humans exposed at plausible environmental levels of exposure.

And finally, the comparative potency method is not supported by our current knowledge of how the several agents or technologies cause lung cancer. The differences are likely substantial.

Thus, as a bottom line, it is not possible to derive quantitative estimates of human cancer risks for DPM. It would be appropriate to note that chronic low level exposure to DPM may increase the human lung cancer risk particularly at high levels of exposure in excess of 100 $\mu g/m^3$.

One can use the findings of Garshick et al. (1987) to give perspective to the potential lung cancer risks of exposure to diesel exhaust. They observed a relative risk of 1.41 for railroad workers exposed to diesel exhaust. They observed relative risks of 3.29 and 5.68 for the same population smoking less than 50 pack-years and over 50 pack-years, respectively (See attached table). Thus, diesel exhaust was only very weakly associated with lung cancer as compared to cigarette smoking.

The Garshick et al. (1987) data can, with trepidation, be used to derive relative risks for environmental exposures to diesel exhaust. One adjustment is for intensity of exposure. If it is assumed that the railroad workers were exposed to 500 $\mu g/m^3$ during work hours, this value can be normalized to a continuous exposure concentration of 120 $\mu g/m^3$. A second adjustment may be appropriate for duration of exposure. One approach is to assume all exposures throughout life are equally effective in their association with lung cancer. Using this approach, the excess relative risk of 0.41 is adjusted to 1.43 excessive risk for 70 years of exposure (versus 20 years for the railroad workers). The 1.43 excess risk for 120 $\mu g/m^3$ continuous exposure can be extrapolated downward, again with trepidation, to an excess relative risk of approximately 0.01 for a nationwide average concentration of 1.1 $\mu g/m^3$. Because a

relative risk model is used, the vast majority of the excess cases attributed to diesel exhaust exposure are estimated to occur in smokers or former exposures; very few of the excess cases are estimated to occur in nonsmokers.

Figure 12-1 comparing cancer risks, RfC and Margin of Exposure could be modified to more clearly depict the risks observed in epidemiological studies and then being estimated. (See attached Figure 12.1 with hand-drawn additions). The revised figures show estimated values for the lifetime risk of lung cancer in smokers and non-smokers. The estimated risk for individuals smoking and exposed to diesel exhaust is also shown based on the Garshick et al. (1987) data. I suspect that his estimate of the odds ratio for diesel exposure was largely based on smokers since I suspect he did not have sufficient lung cancer cases in either diesel exposed or nonexposed nonsmokers to derive statistically meaningful estimates of odds ratio.

One point clear from the revised graph is that extrapolations from real data estimates must be made by more than two orders of magnitudes to reach the exposure levels of concern for ambient environmental exposures. As an aside, in examining Figure 12.1, it is not clear to me why the "cancer risk line" at 2×10^{-3} is more than 2 orders of magnitude displaced from the cancer risk line of 1×10^{-4}.

References

Garshick et al. (1987) Am. Rev. Resp. Dis.

McClellan, R.O. (1996). Lung cancer in rats from prolonged exposure to high concentrations of particles: implications for human risk assessment. Inhalation Toxicology 8 (Suppl):193–226.

McClellan, R.O. (1997). Use of mechanistic data in assessing human risks from exposure to particles. Environmental Health Perspectives 105 (Suppl. 5):1363–1372.

CASE-CONTROL STUDY OF U.S. RAILROAD WORKERS

(Garshick et al., Am. Rev. Resp. Dis., 1987)

EXPOSURE CATEGORY	ODDS RATIO (with 95% CI) CASES ≤ 64 yrs	CASES ≥ 65 yrs
Diesel Exposed (20 year)	1.41 (1.06 - 1.88)	0.91 (0.71 - 1.17)
Asbestos	1.20 (0.87 - 1.65)	0.96 (0.81 - 1.20)
≤ 50 pack - years	3.29 (1.57 - 6.93)	4.38 (2.90 - 6.60)
≥ 50 pack - years	5.68 (2.73 - 11.80)	9.14 (6.11 - 13.70)

Note: using 0 - 4 yr diesel as referent group
5 - 19 yr - odds ratio 1.02 (0.72 - 1.45)
≥ 20 yr - odds ratio 1.64 (1.18 - 2.29)

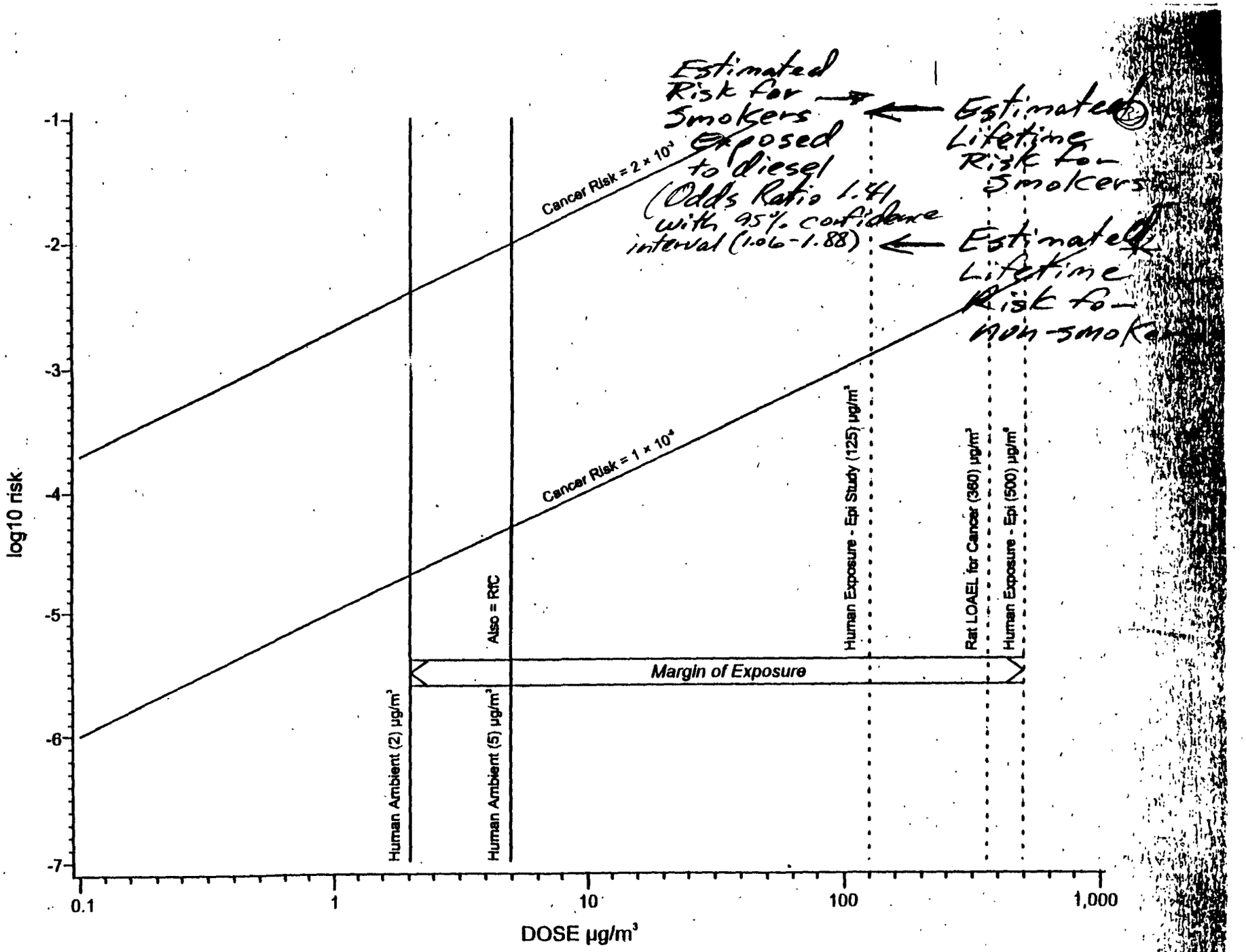


Figure 12-1. Comparison of cancer risks, RfC, and MOE.

CHAPTER 4

Page 4-1 - line 26: Replace "these findings" with "the exceptional findings"

line 33: Replace "total" with "retained"

Page 4-3 - line 8-14: Deposition in the alveolar region is mentioned here, implying that the small diesel particles deposit preferentially in this area. However, tracheobronchial deposition if expressed per unit surface area may even be greater, which may be of significance especially in situations (humans) where mucociliary clearance is impaired.

Page 4-4 - line 34
and
Page 4-6 - line 1: Table 4-1 does not list data on a volume basis which makes this sentence hard to understand unless the deposited mass is also expressed per lung volume.

Page 4-6 - lines 13 and 24: Replace "highly insoluble" ("relatively insoluble") with "poorly soluble"

Page 4-10 - line 6: Replace "individuals" with "coal miners" and add after pneumoconiosis "with presumably high lung burdens of coal mine dust"

Page 4-12 - line 11: It sounds as if only the high dose exposure group resulted in significant lung burdens, but not the other ones, which I am sure is not correct. It would be best to indicate the amount actually found being retained in all dose groups.

CHAPTER 4.3.2.2

Line 4-10: The data described here in this chapter should be summarized in a short table which would make it much easier for the reader to evaluate prolongation of alveolar clearance with exposure concentrations and lung burdens.

Page 4-13 - line 18: Delete the word "generally"

Page 4-14 - line 35: Replace in "aerosols" with "poorly soluble particles of low toxicity"

Page 4-16 - lines 4-9: It should be more clearly discussed that the term "particle overload" relates only to poorly soluble particles of low cytotoxicity and that cytotoxic particles such as

crystalline SiO_2 and effects caused by them in the lung are not part of the overload phenomenon. Also in line 7, it is not clear what surface associated organics in the case of silica mean. Silica particles induce their effects when administered as highly pure particles without any adsorbed material.

Page 4-16 - line 16: In the study by Freedman and Robinson (1988) no attempts were made to diagnosing lung cancers. Thus, this sentence needs to be changed or deleted.

Page 4-19 - line 6: Replace "lymphocytes" with "neutrophils"

Page 4-19 - line 9: Delete the word "significantly" since only 0.001% of the particles were translocated to the lymph nodes within 24 hrs.

Page 4-26 - line 13 and 14: The identical elimination rates of BaP and particles also could indicate that the desorption for BaP is the same as the clearance of particles. This conclusion is also used in lines 21 and 22 of the same page. However, this study was only done over a 7-day period and cannot be used to predict long-term clearance of adsorbed BaP.

Line 30 and 31: It has not been shown by Snipes and Clem and by Oberdörster *et al.* that 15 µm particles can be phagocytized by alveolar macrophages. On the contrary, Oberdörster *et al.* (1997, *Inhaled Particles VIII*) have shown that in mice even 10 µm particles are not phagocytized by alveolar macrophages. Mice were used in the study by Creasia *et al.*

Page 4-28 - line 11: Type I cells are not target cells for long-term effects by diesel particles. Type II cells, however, are.

Page 4-28 - line 25, 26: Retention halftimes for humans can be even higher up to two years as shown by studies in humans by Bailey *et al.* I would also suggest here (line 26) and in other parts of this document to use the term retention in the context of halftime rather than clearance, and to use the term clearance when the actual rate is given or discussed, but not clearance halftime.

Page 4-32 - line 26: Change "inhibited" with "altered"

* * * * *

This dosimetry chapter basically contains the same information as the previous version of the document. However, it should be updated in at least two areas: One is the model that was

described by Stöber *et al.* (POCK model) has now been described as an updated advanced version by Stöber and McClellan (1997) and should be incorporated here. The other potentially important development is the change in diesel engines, at least for trucks, resulting in a significantly decreased output by mass of particles, but at the same time a significant increase in particles of the ultrafine mode. Discussion on the potential health effects of ultrafine particles is ongoing now and it would be useful to incorporate dosimetric aspects of ultrafine particle deposition in this chapter. These particles according to the ICRP model can have an extreme high deposition efficiency in the alveolar region, and their disposition after deposition is also quite different from that of larger particles. This information would be useful to include in a chapter written in 1998.

* * * * *

Chapter 7: Carcinogenicity of Diesel Emissions in Laboratory Animals

Page 7-3 and following, Table 7-1: Add "inhalation" to the title of this table.

Page 7-10 - lines 1 and 2: The issue of the squamous cyst may need to be discussed again in view of the publication by Boorman *et al.* (*Toxicologic Pathology* **24**: 564-572, 1996) which is a summary report of a meeting of international pathologists describing a consensus of how to classify squamous cysts.

lines 8 and 9: The logistic regression model described here is presumably that by Mauderly *et al.* (1987) which needs to be referenced. It may also be useful to show a figure of this regression model in the document.

Page 7-12 - line 9: The TiO_2 used in this study was ultrafine TiO_2. The animals exposed to these high concentrations of ultrafine TiO_2 and carbon black showed also lower survival compared to the diesel-exposed animals which the authors attributed to the high inhaled concentration of these particles resulting in increased general toxicity.

Page 7-13 - lines 4-13: The effects described here on prolongation of alveolar clearance should also be presented in Chapter 5.

Page 7-17 - line 15: The development of mesotheliomas in the diesel-exposed rats is mentioned here. This is not indicated in Table 7-1, and if significant, would be a finding worth discussing. Was there any fiber exposure ongoing at that time in this contract laboratory?

Page 7-19 - lines 31-34: TiO_2 used in this study was ultrafine: Increase of the ultrafine TiO_2 concentration and carbon black concentrations resulted in high toxicity in the mice such that the exposure duration of the whole study had to be shortened to a total of 13.5 months of exposures. This should be mentioned here in the report since it reflects the high exposure concentrations and lung burdens used in this study.

Page 7-26 - Table 7-2: Include in the title that treatment was done by surgical lung implantation.

Page 7-28 - line 6: Replace "MMAD" with "surface area"

Page 7-29 - Table 7-3: The source should be indicated for the study, Dasenbrock *et al.*, 1996.

If available, a characterization of the different carbon black used in the different studies should be included with respect to particle size and surface area.

* * * * *

A general comment for the whole document relates to the lack of including newer data. For example, in Chapter 5, animal studies on effects of hypersensitivity reactions after diesel exposure are missing; Chapter 10 should include a more detailed description and discussion on the inflammatory mechanism of carcinogenicity for which there are a number of recent relevant publications by Driscoll *et al.*

Additional Comments:

Chapter 6: I suggest to include a range for the RfC (5-16 mg/m^3) because of the questionable use of the Data Base Uncertainty factor.

Chapter 9: The studies listed on pages 9-3 and 9-4 should all include the doses or inhaled concentrations that were used. This would put the results into perspective, and it would be helpful to point out the high doses (*in vitro* or injected) which resulted in positive effects. Missing in this chapter are our studies reported by Driscoll *et al.*, (1996) with carbon black showing secondary genotoxicity (HPRT mutations) after subchronic inhalation in rats; and additional studies with *in vitro* exposures of epithelial cells to inflammatory cells from in vivo exposed animals resulting in HPRT mutations; and the blocking of these mutations with antioxidants (all studies by Driscoll *et al.*). Taken together these studies strongly suggest an inflammatory mechanism of mutagenesis in particle overload situations. This information should also be presented and included in the Mechanism Chapter 10.

Chapter 10: Page 10-4, lines 9-17: Include Driscoll *et al.* studies mentioned above, *in vivo, in vitro* and *ex vivo* studies which are key for plausible mechanism.

Page 10-17, line 5: Inflammation, however, appears to be a prerequisite for mutagenicity.

Line 6/7: Point out the high dose in Riebe-Imre study.

Line 9: PTFE particles are highly toxic and not a surrogate for diesel particles, a cautionary note should be added.

Page 10-23, line 19/20: The slower particle clearance in humans allows for greater efficiency of extraction: This statement is in contract to what is discussed in the dosimetry chapter on page 4-28.

Line 21/22: DE is effective in non-overload conditions: Which study is that?

Lines 25-29: The "low" doses in the Riebe-Imre study are not that low, the fact that no cytotoxicity was seen does not mean that the *in vitro* dose was low.

Chapter 11: Page 11-16, Table 11-6: I suggest to express risk estimates per μg organics on the diesel particles. This estimate then can be compared to cancer risk estimates derived from a good data base of humans exposed to PAH, such as coke oven workers. This will allow a comparison between diesel-associated organics and others and provide a test about how reasonable the diesel-derived risk estimate is.

Chapter 12: I suggest to define the estimated risk as "hypothetical risk", indicating the uncertain nature. In addition, a listing of the uncertainties of using the high dose rat data for predicting low dose human risk should be included as an explanatory note for the hypothetical risk.

G. Oberdörster
5/8/98

Bill Pierson
5/13/98

Chapter 1

Is it true that the fraction less than 2.5 μm that are implicated in the cancer and noncancer effects observed from diesel particulate emissions exposure? Where is the support for this statement (lines 1-1-33 to 1-2-2) ?

Is it really true that "companion comprehensive characterizations _____" are not included in the assessment? I thought some of them were, in Chapter 2.

Chapter 2

1) A glaring weakness is that there is no mention of the work of Baumgard and Johnson (1996) or of Bagley *et al.* (1996). In that work they claim to have found with present-day engines there is a 10^3-fold increase in fine particulate matter compared to past engines. It is as if current engines, supposedly cleaner than in the past, give huge amounts of ultrafine (0.0075-0.46) particles. The nature of these particles is not identified but Baumgard and Johnson think it may be H_2SO_4. Kittelson, on the other hand, believes that the same is true of the older engines as well depending on how the sampling is carried out, and he cites Kittelson *et al.* (1988) and the work of Paul Harrison in support. Currently this is an intense issue among the diesel manufacturers and a Coordinating Research Council initiative is getting underway. None of this is mentioned in Ch. 2 except indirectly perhaps at the bottom of p. 2-8 and top of p. 2-9 and the end of the exposure perspective (section 2.6, p. 2-57, l. 20 to p. 2-58, l. 8), and there they say that basically they recognize that they do not want to get into it. But I think they have to, discussing at least the papers mentioned above.

They do acknowledge the dilution of diesel exhaust under roadway conditions as opposed to dilution in a dilution tunnel is an important factor to consider. As stated on p. 2-26, l. 7-10 "This discrepancy leads to slightly different particle size distributions under real driving conditions than those predicted from laboratory data (Kittelson and Dolan, 1980); for example, because of slower coagulation processes, more particles in the Aitken nuclei range (≤ 0.08 μm diameter) may be expected under typical roadway conditions". See also pp. 2-45, 1.23-30. Also see Dolan, Kittelson, and Pui (1980).

2) In fact, all but about 5 references are dated 1990 or before. In the next few days I will be sending reprints and reprint lists that in my opinion should be included. And yet, on the other hand, there seems to be no awareness (on p. 2-8, for example), of the early work by Kotin, Falk and Thomas (1955) - see complete ref. in Ch. 11-26, line 36 - and others listed at the end of my review.

3) The material on pp. 2-38 to 2-43 (see sec. 2.4.2.1.7, and 2.4.2.2 and 2.5.3) are important for the rest of the document and yet seem to have been overlooked by all of the writers of the rest of the document. In sec. 2.4.2.1.7 it is described how, in the gas phase, 2- to 4-ring PAH's emitted

by diesels into the ambient air are attacked by a 2-step process involving OH or N_2O_5 followed by NO_2 to produce airborne mutagens in the gas phase not found in exhaust emissions, such as 2-nitrofluoranthene and 2-nitropyrene (instead of 3-nitrofluoranthene and 1-nitropyrene); see Table 2-18 (p. 2-52). Eventually, these compounds, though formed in the gas phase, will find their way to the particle phase (sec. 2.4.2.2.2 would probably be a good place to point this out).

Thus, "a knowledge of diesel emissions at or near their sources is not sufficient to fully assess the impact of these emissions on human health ... However, data on how diesel exhaust contributes to exposure levels for these secondary pollutants are currently lacking" (p. 2-56). The point is also made on p. 2-43 that "the formation of nitro-PAHs during sampling may be an important problem for diesel particulate matter because of the presence of NO_2 and HNO_3. In fact, Gorse, as mentioned on p. 2-47, found in the Allegheny Tunnel that 1-nitropyrene was much lower than it is in dilution-tube sampling. Differences listed on p. 2-45 should serve as a warning on this issue:

- dilution ratio
- temperature
- residence times
- mixing with other vehicle exhausts
- mixing with ambient pollutants

In summary this whole section of Ch. 2 (and the Exposure Perspective and the Summary) carries the message that as one moves away from the dilution tube and especially as one moves downwind and into the real world and allows processes (see pp. 2-28 and 2-40);

- photolysis
- reaction with OH
- reaction with ozone
- reaction with HO_2 and H_2O_2
- reaction with NO_3, N_2O_5, NO_2, HNO_3, HNO_2, H_2SO_4

we enter an area that could be important but we actually don't know - and the other chapters of the criteria document do not reflect any of this at all.

4) However, there is another problem in that gasoline-powered vehicles emit PAHs also. If we start down the path of downwind effects, then the problem suddenly becomes one of much more than diesel effects.

5) What do the nitro-PAHs transform into inside the body? This is discussed in Ch. 10 Sec. 2 which fact should be mentioned in Ch. 2.

There are a number of minor comments:

Beginning in this chapter and continuing all the way through the document, DE and DPM are used. I saw DE defined as diesel exhaust and DPM defined as diesel particulate matter but they

are often used to refer to what is apparently the same thing. I suggest that the document be gone through to fix this.

p. 2-2, ll. 4-36 and p. 25, l. 35: The same lubricating oil is used in gasoline engines. Should this not be pointed out? Why is lubricating oil not as much of a problem in SI engines; the consumption rates are similar between SI and diesel.

Sec. 2-2. Somewhere in this section might be a better place than in Chapter 12 (p. 12-38, l. 1-4) that most engine modification steps to reduce particulate emissions increases NO_X emissions (with its own set of problems as listed in Chapter 12), and vice versa.

Also in Chapter 2, probably in Sec. 2-2, there should be some discussion of the remanufacturing process for diesel trucks. Because of remanufacturing and also the long lifetime of a diesel relative to gasoline engines, the time between emission-reduction (or any other) step is much longer than we are used to thinking of based on gasoline engines. And I do not know how much freedom there is to implement steps that would improve emissions at each remanufacture. Obviously this relates to the recent discussions from Johnson *et al.* about newer engines putting out completely different particles. It affects how long it takes for steps taken to improve emissions to show up on the road, or whether if there is a big change how long we can expect Chapters 4-12 to have any bearing on anything.

p. 2-3, define HEI.

p. 2-6, line 25, why is carbon never formed at < 1900° K?

p. 2-7, ll. 16-21: Hampton *et al.* (1983) had a treatment of this, showing that the gas/particle phase apportionment essentially followed Raoult's Law (see Fig. 8 of Hampton *et al.*).

p. 2-7, ll. 24 to 2-8, l. 3: Truex *et al.* (1980) showed that 1) the particulate sulfate in diesel exhaust is H_2SO_4 and 2) as the S content of the fuel goes down the % H_2SO_4/SO_2 ratio goes up. This paper is discussed on p. 2-10, lines 10-13, but it is not mentioned in the latter case that the % H_2SO_4/SO_2 goes up as fuel S goes down.

p. 2-8, lines 4-11: Shouldn't this have a "2.2.3.3 Oxidation of Nitrogen Oxides" title on it? It does not belong under "Oxidation of Sulfur Oxides". Also the Harris *et al.* measurements of HNO_3 are mentioned but those of Okomoto *et al.* are not; but on p. 2-10, ll. 14-18 they are all mentioned. Since NO_X and HNO_3 are gases, perhaps all of the discussion on p. 2-8, l. 4-11 should be moved to, and combined with, that on p. 2-10, ll. 14-18.

p. 2-8, line 25, can you give an idea of how much mutagenicity has been found?

p. 2-8, line 35 to 2-9, line 3: If the diesel emissions currently used are different from those that may have occurred in the past, this is a real quandary for the whole document (which I think we all recognize).

Table 2-3: It is very difficult to figure out which numbers come from where. What is ref. h - it must be one of f and g. What does the [g/km] mean at the top, since only one set of numbers is given?

The numbers in Table 2-3: There is something seriously wrong. The original references for n-decane and n-dodecane (n-undecane is left out), toluene, ethylbenzene and naphthalene give numbers between 11 and 8666 times the numbers given here. The value for benzene is a factor of at least several hundred off from any reasonable number.

Table 2-3: Text at bottom of p.2-10 and top of p. 2-12 implies that all data in Table 2-3 were obtained on the Federal Test Procedure. The data from the tunnels were not on the Federal Test Procedure.

Table 2-3: I am not sure why U.K. data for noncatalyst cars were used. There should be plenty of data from the U.S.

p. 2-13, l. 5: "Table 2-3 lists the emission rates for exhaust pipe emissions only". But this is not true since Table 2-3 lists data from vehicle tunnels. If it is true (l. 5-7) that 30-60 % of total HC emissions from passenger gasoline vehicles are from fuel evaporation, then in Table 2-3 there should be a note and the tunnels should be segregated from the others.

p. 2-13, ll. 22-23: Carey and Cohen are cited as if they are included in Table 2-3 but they are not.

p. 2-12, ll. 5-29: Subsequently we have carried out an intensive tunnel experiment and now have considerable data to add to this discussion and to Table 3, if you want at this late date to add it. In particular we now have the data for C<8 which would make up for the deficiency mentioned on lines 27-29. (See Pierson *et al.*, Atmos. Environ. **30**, 2233-2256; Sagebiel *et al.*, Atmos. Environ. **30**, 2287-2296.) However, see the comment below on p. 2-47, ll. 11-31.

Table 2-4: The g/mi numbers for heavy and light-duty diesels from Williams *et al.* sound a bit high. Is it appropriate to use data from Australia? Do we not have data from SWRI (indeed sponsored by EPA) that would serve?

Table 2-4: I think ref. d had numbers for more than just OC. In particular, we had 84 ± 14% carbon in the total particulate mass from diesels, 67 ± 42% from SI, which should be added to your row labeled TC (% w/w) in Table 2-4.

p. 2-17, ll. 1-2: How does this statement affect the statements on p. 2-13, l. 36 and p. 2-14, l. 1?

p. 2-19, ll. 22-24: There is much older work, starting with Kotin, Falk and Thomas (see Chapter 7 refs., p. 7-46, l. 50) which is not cited here.

p. 2-23, l. 19-20: What is the significance of phenazine and phthalic anhydride being identified, or is it just an observation?

p. 2-23, ll. 4-7: The paper by Salmeen, listed in your refs. (p. 2-67, l. 23), is far more pertinent than the Schuetzle paper cited here. The latter paper was dealing with material recovered after indefinite times from the wall of a dilution tube and may or may not represent diesel exhaust.

p. 2-24: There is another much more serious problem than blow-off. There is also degradation. Far more serious is the problem of degradation into other products. This was shown in a vehicle tunnel by Lee *et al.*, ref. 33 (see your list of refs., p. 2-64, ll. 33-36).

Fig. 2-2: Since presumably the vapor/particle distribution depends critically on the amount present, could we draw the Figure to show the amounts present in each case, or if that is too much trouble, label the right end of each bar with the amount present? That would convey a lot more information.

p. 2-25, ll. 9-12: I believe that Wm. Wilson has some work on this. You should check with him and, if appropriate, add a reference.

p. 2-32: Fix l. 11. The letters on ll. 16-19 and below on the page are too little to read.

p. 2-30 to 2-34: Where does that leave us? Is all of this necessary?

p. 2-33, l. 16: What does radical (a) refer to?

p. 2-33, l. 23: What does Table 2-3 refer to here? I do not recognize anything in Table 2-3 (p. 2-11) that has to do with what we are talking about here.

p. 2-34: Table 2-13 is out of place. It is not introduced in the text until p. 2-40, l. 14. The ref. to Table 2-13 on p. 2-33, l. 12 is an error since there are no alkenes listed in Table 2-13.

p. 2-36, ll. 21; p. 2-37, ll. 3, 7, 28 ff - all too little to read.

p. 2-40, l. 23-33: Why should this list and the list on pp. 2-28, l. 8-24 be any different?

p. 2-41 to p. 2-42 or p. 2-43: It is beginning to seem as if there is a lot of attention being given to PAHs - and maybe not enough to other constituents.

p. 2-43, ll. 4-7: Since Gorse got much lower 1-NP in the vehicle tunnel, as you mention elsewhere, I am skeptical of the < 10-20 % cited here. Also, where did the 43° C come from; in dilution tube sampling the temperature can be as high as 52° C?

p. 2-43, l. 12-36: You can get the same sort of thing happening under much less serious conditions. This has already been mentioned on the comment on p. 2-24. Again, the Lee reprint (your ref. on p. 2-64, ll. 33-36) shows this.

p. 2-45, ll. 28: Five seconds sounds too long. With a flow of 450 cfm (typical for a dilution tube) with a 1 ft^2 cross section and 25 ft. from entrance to sampling point, residence time would be more like 0.05 seconds (check my math).

p. 2-47, l. 11-31 and Table 15: You many not at this late date want to include the references mentioned above in p. 2-12, ll. 5-29 but I mention it again here. In any case, there seems to be some overlap between Sec. 2.3.1 and Sec. 2.5.1.

p. 2-49, ll. 15-16: There is a recent paper by Miguel *et al.*, Env. Sci. Technol. **32**, 450-455 (1998) which could be cited here.

Table 2-18: Is this the gas-phase only?

p. 2-53, l. 11: I do not see anything in either trace on p. 2-54 labeled 3-NF (probably too low?).

p. 2-53, l. 18-19: Doesn't the 2-NF/2-NP ratio depend on the concentrations of fluoranthene and pyrene?

p. 2-57, l. 9-16: This work has now been published. [Gertler,A.W.; Sagebiel,J.C.; Dippel, W.A.; Farina,R.J. (1998). Measurement of dioxin and furan emission factors from heavy-duty diesel vehicles. JAWMA, **48**: 276-278]. But it seems out of place to be reporting it here; it should be reported somewhere in sec. 2.2 or 2.3. Also the subject is taken up on p. 12-30, l. 26 ff. These should be combined into one discussion. However, p. 12-30 has several misstatements. It was the Fort McHenry Tunnel (not Baltimore Harbor Tunnel) conducted by the Desert Research Institute (not Desert Research Laboratory).

p. 2-59, ll. 11-14: This statement may be untrue once the results of the NFRAQS (Northern Front Range Air Quality Study) come out. Stay tuned.

In general I believe that Chapter 2 has a great deal of material in it and is definitely worth updating, if for no other reason than to serve as a warning about how lacking the research covered in all the subsequent chapters is.

References to insert in 1. 2

Baumgard,K.J.; Johnson,J.H. (1996). The Effect of Fuel and Engine Design on Diesel Exhaust Particle Size Distributions. Warrendale, PA: Society of Automotive Engineers; SAE technical paper no. 960131. Reprinted from Diesel Exhaust Aftertreatment 1996 (SP-1140).

Bagley,S.T; Baumgard,K.J.; Gratz,L.D.; Johnson,J.H.; Leddy,D.G. (1996). Characterization of Fuel and Aftertreatment Device Effects on Diesel Emissions. Health Effects Institute Research Report Number 76.

Begeman,C.R. (1962). Carcinogenic Aromatic Hydrocarbons in Automotive Effluents. Paper No. 440C presented January 1962 at the SAE Automotive Engineering Congress. SAE Technical Progress Series Vol. 6, "Vehicle Emissions", New York: Society of Automotive Engineers Inc., 1964.

Dolan,D.F.; Kittelson,D.B.; Pui,D.Y.H. (1980). Diesel Exhaust Particle Size Distribution Measurement Techniques. Warrendale, PA: Society of Automotive Engineers; SAE technical paper no. 800187.

Kittelson,D.B.; Kadue,P.A.; Scherrer,H.C.; Lovrien,R.E. (1988). Characterization of diesel exhaust particles in the atmosphere. Final report to Coordinating Research Council AP-2 Project Group, March 1988.

Moore,G.E.; Katz,M. (1960). Polynuclear Aromatic Hydrocarbons in the Particulates of Diesel Exhaust in Railway Tunnels and in the Particulates of an Urban Atmosphere. Int. J. Air Poll. 2, 221-235.

Tebbens,B.D.; Thomas,J.F.; Mukai,M. (1963). Particulate Air Pollutants Resulting from Combustion. From ASTM Special Publication No. 352, Symposium on Air-Pollution Measurement Methods, presented at the Fourth Pacific Area National ASTM Meeting, Los Angeles, Oct. 5, 1962 (published 1963 by ASTM).

Chapter 4

p. 4-2, l. 29: It is interesting that electrostatic precipitation is mentioned. This is an area that has not been thought of as much as it should be, given that there have been many references reporting considerable + and - charges on diesel exhaust. In fact it might be useful to include a few.

p. 4-4, l. 9: What are the obligatory nose breathers (name).

Table 4-1: I do not understand

p. 4-7, l. 26: ^{98}Tc has no metastable state (^{98m}Tc). Something wrong.

Fig. 4-3: Redraw. Lines too faint.

Sec. 4.3.2.2 seems all to have to do with rat data although it is called "alveolar clearance in animals" and I thought there is something wrong with rat data (see p. 10-2 11.11 - 1 and 2)

p. 4-14, l. 7 and 9: AM has been introduced without any definition (Alveolar microphages).

p. 4-18, l. 9 and several places on p. 4-20: What are Type 1 cells?

p. 4-18, l. 23 to 33: The word *endocytosis* is used three times. I went to the dictionary and then to the medical dictionary and I still don't know what it is. Put the cookies on the lower shelf.

p. 4-26, l. 5: I do not see any evidence about extractability etc., of the 2-nitropyrene formed in air from diesel exhaust (see comments in Chapter 2). Is there no such work?

p. 4-27 all of Sec. 4.4.3: How does extraction of nitro-pyrene etc. compare with something like B(a)P; how soluble and how strongly bound to elemental carbon?

p. 4-28, line 8: What is a target site?

p. 4-29, l. 31: What is solvent green?

p. 4-31, l. 10-11 and 15-16: The idea of the effect being proportional to the surface area of the particles is very worth mentioning.

p. 4-31, l. 25-27: The lack of dosimetric factors for the gas phase seems a weakness of studies conducted so far; after all, there are carcinogens in the gas phase. How do you get at them? Particularly (see Ch. 2) the 2-NP and 2-NF in the ambient air (not present in diesel exhaust but made from diesel exhaust in the ambient air)? Eventually these compounds do find their way to the particle phase. (This is more a criticism of the state of the science being reviewed than it is of the reviewer.)

p. 4-32, ll. 28-29: What animals are being discussed - more likely to be awake etc.

Chapter 5

p. 5-3, ll. 11 to 13 are virtual repetitions of ll. 8 to 10.

p. 5-7, ll. 19 to 21: "The ...exposure" - I do not see the support for this.

p. 5-9, l. 7: How is it possible to expose stevedores to diesel exhaust particulate without exposing them to NO_2?

p. 5-11, ll. 15-25: What was the difference between the two Edling studies that such different results were found?

p. 5-11, ll. 33-34: Epidemiology is discussed in Ch. 8. Why then here? Has there been no effort to edit these chapters and see that they conform (this is not the first time that I see evidence that this has not been done). Also see p. 5-82, l. 8.

p. 5-13: I very much like the use of Tables here and throughout the document, to pull together all of the health effects of one kind or another. These are extremely helpful.

p. 5-17, l. 13: Do we need Appendix A?

p. 5-18, l. 6: vascular, not vacular.

p. 5-19, l. 8-11: The statement seems too strong since diesel particulate is only a small part of the particulate matter to which the average person is exposed.

p. 5-23, ll. 34 ff: This is important to emphasize.

p. 5-24, l. 4: What does frank mean?

p. 5-24, l. 12: Respiratory, not resoiratory.

p. 5-33, ll. 25-26: What are "treatment-related"?

p. 5-45, l. 3: What is chemotactic?

p. 5-53, ll. 7, 12, 17, 19, 20, 23: What is BALF - defined on p. 5-42, l. 21 but I think that is too far away.

p. 5-86, l. 34 (and also in Chapter 4 p. 4-1, l. 31 and in Chapter 6 p. 6-3, l. 32) we speak of a "carbonaceous core". This is quite misleading and may not be very helpful as we think of diesel exhaust extractive processes in the lung. The particle is not constructed like an onion with an organic skin around a carbonaceous core of carbon. Rather, the carbon is linked in chains or aggregates like a bunch of grapes, with the organic material filling in the interstices.

Chapter 6

p. 6-2, l. 1: Take out the comma after research.

p. 6-3, ll. 6-7: "The weight of evidence from the available toxicological data on diesel exhaust indicates with high confidence that inhalation of diesel exhaust can be a respiratory hazard, based

on findings in multiple controlled laboratory animal studies in several species with suggestive evidence from human occupational studies." From context, this refers to the two previous chapters, or else this chapter is out of place. So I re-studied these chapters. Chapter 4 is largely about rats only, usually in an overload condition. Chapter 5 gave data for humans exposed to gross diesel exhaust (usually without isolation of the particulates); I see a statement, "The overall conclusion of these studies is that reversible changes in pulmonary function in humans can occur in relation to diesel exhaust exposure", without offering any support; I see nothing in the long-term exposures, and in fact quite the opposite. It is stated (p. 5-11, ll. 26-27), "The absence of reported noncancerous human health effects, other than infrequently occurring effects related to respiratory symptoms and pulmonary function changes, is notable." Table 5-1 (Human studies of exposure to diesel exhaust) showed conflicting evidence of short-term respiratory reactions (cough, phlegm, etc.) to diesel exhaust, but the patterns were not consistent or in some cases attributed to other causes. The animal studies (Table 5-2. Short-term effects of diesel exhaust on laboratory animals) definitely show effects (largely attributable to CO and NO_2 - see bottom of p. 5-23 ff.) But "Little evidence exists, that subchronic exposure to diesel exhaust impairs lung function" (p. 5-24, ll. 11-12). Chronic exposures (Table 5.3 and 5.4) often indicate no effect. Effects on pulmonary function (Table 5.5) again are conflicting. Histopathological effects (Table 5-6) seem to agree on inflammatory changes, otherwise results are all over the place. Effects of exposure to diesel exhaust on the pulmonary defense mechanisms of laboratory animals (Table 5-7) are very mixed. The effects of exposure to diesel exhaust on the immune system of laboratory animals (Table 5-8) seems to show nothing. Same for effects of exposure to diesel exhaust on the liver of laboratory animals (Table 5-9). Same for effects of exposure to diesel exhaust on the hematological and cardiovascular systems of laboratory animals (Table 5-10). Same for effects of chronic exposures to diesel exhaust on serum chemistry (Table 5-11). As for the effects of chronic exposures to diesel exhaust on microsomal enzymes of laboratory animals (Table 5-12), again the results appear to be mixed. There does seem to be an effect for chronic exposures to diesel exhaust on behavior and neurophysiology (Table 5-13). For effects of chronic exposures to diesel exhaust on reproduction and development (Table 5-14) there appears to be little or no effect. "The most readily identified acute noncancer health effect of diesel exhaust on humans is its ability to elicit subjective complaints of eye, throat and bronchial irritation and neurophysiological symptoms such as headache, lightheadedness, nausea, vomiting, and numbness and tingling of the extremities" (p. 5-81, ll. 7-10). "Studies on the acute health effects of exposure to diesel exhaust in humans, experimental and epidemiologic, have failed to demonstrate a consistent pattern of adverse effects on respiratory morbidity; the majority of cases offer, at best, equivocal evidence for an exposure-response relationship." My question is: In view of all this, how can one honestly make the statement at the top of this paragraph?

p. 6-5, l. 14: I raise again the question of whether this chapter is out of place. Carcinogenicity does not get discussed until Chapter 7 and 8.

p. 6-13, ll. 19-20: Again the same question.

p. 6-26, ll. 30-32: Again the same question. This chapter seems to belong after Chapter 8.

Chapter 7

p. 7-1, ll. 19-21: How does this square with statements elsewhere that the unextracted core is the only active part of the PM? (See for example p. 7-28, ll. 14-18.)

p. 7-2, ll. 7-10: What health assessment documents are referred to here? (give ref.)

p. 7-2, ll. 13 ff: These are all rat studies. Therefore, is the statement on p. 7-10, ll. 16-21 any good? Is the whole section of any import? I keep hearing that the rat data should be rejected because of overload. Is this true or not?

p. 7-18, ll. 30-32: This is just nonsense. You do not decide to accept a finding as statistically significant because the signal is supposed to be low anyway. If it isn't statistically significant, then you can't talk as if it is.

p. 7-44, ll. 24-26: I believe the statement, "In summary, based on positive inhalation exposure data in rats and mice, intratracheal instillation in rats, and injection or skin painting in mice and supported by positive mutagenicity studies, the evidence for carcinogenicity of diesel exhaust is considered to be adequate." But at this point, mutagenicity studies have not been discussed yet (they come in Chapter 9). So the statement, which is important and much more to the point than some of the stuff in Ch. 12, is a statement that is worth repeating at a prominent point near (perhaps in Ch. 12), and perhaps at the end of, the criteria document.

Chapter 8

Beginning with this chapter and sprinkled throughout all of the subsequent chapters, there are 17 (!) references to Garshick and his work. I believe that this represents in part a deficiency in organization of the chapters. I have already referred to other instances which indicate an organizational problem.

Nonetheless, I do like in this chapter the organization by each set of authors (Sec. 8.2, and also Sec. 8.3, and Sec. 8.4.

p. 8-33, l. 5,7,8,10,11,12,13,14,17,21: What does (do?) MER mean?

p. 8-52, l. 5: What are dorsopathies? Back problems?

p. 8-54, ll. 30-32: "Animal data suggest that diesel exhaust is a pulmonary carcinogen among rodents exposed by inhalation..." This Chapter 8 is a review of Cohort studies, case-control studies of (human) lung cancer, case-control studies of (human) bladder cancer. I do not see

what the statement in quotes is doing here - even if it is true as in another form was discussed earlier. But I agree with what it leads into (p. 8-54, ll. 32-35).

p. 8-62, ll. 24-32: I agree.

p. 8-63, ll. 2-3: "Among the 10 lung-cancer case-control studies reviewed in this chapter, only 2 studies did not find any increased risk of lung cancer." This is a distortion. The fact is that 2 found no evidence and indeed opposite evidence, 7 found no evidence one way or the other, and 3 found positive evidence. The statement in quotes leaves the impression that 8 out of 10 studies found a statistically significant increase in lung cancer.

p. 8-63, l. 20: And in addition the document says the results in these studies are underestimated at best. I do not understand this and I think there should be an explanation

p. 8-64, ll. 6 to 26: I agree that the best study was that of Garshick. I would not put Steenland *et al.* (1990) into the same category.

p. 8-64, ll. 33 ff: I have the same problem with the discussion of bladder cancer, of which you say 4/7 of them found increased risk in occupations with high potential exhaust exposure. I believe your ending sentence on p. 8-65, ll. 9-13 takes care of bladder cancer.

p.8-69, l. 41 to p.8-70, l. 6: What does the equivocation mean?

Chapter 9

My only comment is that several papers from Ford have been cited but perhaps the most important one (Pierson *et al.*, Mutagenicity and chemical characteristics of carbonaceous particulate matter from vehicles on the road, Env. Sci. Tech. **17**, 31-44 [1983]) probably should be included because it is on-road.

Chapter 10

p. 10-1 and elsewhere: DE and DPM seem to be used interchangeably. If there is a difference, it should be clarified; if not, then use one or the other.

p. 10-1 and following: I thought the rat data were to be ignored (because of reasons stated on p. 10.2, ll. 1-2).

p. 10-1, lines 14-15: "Epidemiologic data suggest that there is a small increased cancer risk in humans following long-term exposure to diesel exhaust". Again, in Chapter 12 - line 19-20: "Epidemiologic data are strongly suggestive of a carcinogenic hazard to the lung under

occupational exposure conditions". These statements seem inconsistent. But now look at Ch. 8 which deals with the epidemiologic data. Some of these studies turned up negative results, others had some very serious limitations (like not controlling for smoking), some had too little power to mean anything, etc.; only the Garshick 1988 study among the cohort studies was convincing. The case-control studies again come down to a study by Garshick (1987). Finally, the case-control studies for bladder cancer, sec. 8.4, had many limitations; the statement (p. 8-63, l. 2-3) that "among the 10 lung cancer case-control studies reviewed in this chapter, only 2 studies did not find any increased risk of lung cancer" is a distortion. According to my reading, only 2 showed any support, and the rest were either negative or produced nothing significant one way or the other. Similarly, "of the seven bladder-cancer case-control studies, four studies found increased risk in occupations with a high potential diesel exhaust exposure". This is a distortion. The fact is that of 7 cases given, five gave no support, one gave positive support, and one appears to be positive or mixed. Finally, on p. 8-70 it is stated in summary, "based on the human evidence alone, diesel exhaust is close to being a known human carcinogen". I have a hard time reconciling these various quotes.

When these problems were discussed at the meeting, some felt that statistically insignificant numbers all lying on the same side of zero can be taken to signify a positive effect. I confess to a good deal of discomfort with that. I would rather put my faith in the studies by Garshick which are significant and in any case, I still maintain that the statements, "among the 10 lung cancer case-control studies reviewed in this chapter, only 2 did not find any increased risk of lung cancer," and "of the seven bladder-cancer case-control studies, four studies found increased risk in occupations with a high potential exhaust exposure," are both distortions for the reasons given above - I would even say gross distortions.

p. 10-3, line 9: What are athmyic mice? (Missing the thymus gland? What for?)

p. 10-4, l. 1: Add a reference. Also, tie it to the material on p. 2-15, l. 15 to p. 16, l. 2 and conform. They should all say the same numbers and have the same refs., etc. in both places.

p. 10-4, l. 25: How do you know it is surface-area-associated?

p. 10-11, ll. 1-36 and following page: See p. 2-52; 2-NF is probably more appropriate to worry about.

Chapter 11

p. 11-1, ll. 2-4: The presence of known carcinogens such as B(a)P had been known since 1955. What Huisingh *et al.* did, in 1978, was to show that diesel exhaust contained substances that did not require S9 activation to cause a positive Ames result. The compounds known up to then would not have done that. So therefore there were more compounds that had not been identified. Some of them eventually proved to be very "hot".

p. 11-1, ll. 11-12: Forgot to mention Chapter 9 mutagenicity.

p. 11-1, ll. 31-33: Is it not true that many, even most, of the positive studies also suffered from the same methodologic limitations?

p. 11-2, l. 30 to p. 11-3, l. 19: Apparently we have IARC concluding that the evidence for carcinogenicity of whole engine exhaust in experimental animals was adequate but the evidence in humans is limited. This is said to be in agreement with the conclusion of EPA. Under EPA's Proposed Guidelines diesel exhaust is considered a likely carcinogen by the inhalation route of exposure and is considered to be at the upper end of this grouping.

p. 11-4, line 9: such as dinitropyrene

p. 11-6, ll. 1-2: "The potency of the other diesel emission samples was not estimated directly because of the weak response in the skin tumor initiation test. I do not understand this statement, or what follows. On the face of it, it sounds as if the potency test was rigged. The material immediately following does not help (or does not help me).

p. 11-10: Why is the Garshick data being discussed here? It has already been taken up in Ch. 8 and used in Ch. 10. Is there a plan to resolve the Dawson-Crump disagreement on p. 11-10, line 22-31?

p. 11-17, ll. 25-26: If cancer induction in the rat bioassays was observed only under particle-overload conditions, why are we continuing to use the rat data? See p. 11-19, ll. 11-28; p. 11-20, ll. 3-10; and 11-21, ll. 3-[illegible].

p. 11-22, l. 20: "DE is considered to be a probable human carcinogen." This conflicts with Chapter 10 p. 1, l. 14.

p. 11-23, ll. 9-10: Something wrong with the sentence.

p. 11-23, l. 10: What is a MLEs? (See also p. 12-26, ll. 6 and 7).

p. 11-23, l. 22: I think we decided this is upper-bound, not lower-bound.

Chapter 12

p. 12-1, l. 19: Is the word "strongly" too strong?

p. 12-2, l. 15: What sulfur compounds are carcinogenic?

p. 12-2, l. 22-24: This will always be a bug-a-boo as long as the technology is changing rapidly but certainly is true right now.

p. 12-2, l. 27 ff: Needs to be always kept in mind in all of this.

p. 12-5, ll. 17: "Current data do not support confident identification of health hazards other than for the respiratory system." I think this is a fair statement and it certainly reflects where I come out on all of this.

p. 12-8, l. 19: You have already MOA as standing for mode of action (see many times on previous page). You should not write it out here.

p. 12-10, ll. 8-9: I agree that "the most convincing evidence that exposure to DE can induce lung cancer in humans comes from case-control and cohort studies among U.S. railroad workers and truck drivers". But I also agree that it does not deserve to be classed as a "known" human carcinogen (p. 12-11, l. 23) - in fact I might quibble with "highly suggestive" on p. 12-11, l. 22. (How about just suggestive?)

p. 12-13, l. 33 and p. 12-14, l. 5: I don't see the difference between "very likely" and "probable". (I would see a difference between "likely" and "probable".)

p. 12-17, l. 16: Delete to note. It is interesting that what you say is true but not interesting to note it.

p. 12-20, l. 16: 17 $\mu g/m^3$

p. 12-24, ll. 9-22: I gather that the problem is that there is a lot of rat data but they have the overload problem. If you throw out the rat data then you have mice and hamsters left (which I read somewhere in the document have very much less extensive data). So you wish you didn't have to throw out the rat data. But the argument has nothing to do with the amount of data you have; it is all either compromised by the overload problem or it is not. If it is, then you have to throw it out without looking over your shoulder to see what you are left with. In particular the negative findings on rat and mouse data (p. 12-24, lines 12-14) should have nothing to do with the decision on the rat data. You argue for keeping the rat data because they show a response and you know that humans show a response in epidemiologic data. But you are getting the human and the rat to agree for the wrong reasons; the rat is doing it because it is in overload which is a situation that is inapplicable for the human case. I think the only scientifically defensible procedure (if I understand the situation correctly) is to throw out the rat data if it is compromised by overload and to make your case with what you are left with. If this raises the estimated risk (p. 12-24, l. 34), then so be it.

p. 12-26, ll. 6-7: What are MLE? (Same question as earlier in Ch. 11 p. 11-23, l. 10).

p. 12-27, l. 22: I did not initially recall any discussion about exacerbation of asthma. Perhaps it should be noted here where that is discussed (p. 5-6, ll. 1-2; p. 5-18, ll. 27 ff; p. 12-34, l. 27,; anywhere else?)

p. 12-33 ff: This is pure speculation and should be left out. In the present document we are supposed to be dealing with what is known, not what is not known.

p. 12-29, ll. 14-18: As I understand it, Cal - EPA has subsequently decided that diesel exhaust (or emissions?) is indeed a toxic air contaminant. The measured or more careful response in the present document is a long way from that. I think that there is a world of difference between the two readings and therefore I would question the characterization on lines 17 and 18.

p. 12-30, ll. 26-27: Please see p. 2-57, l. 9-16 and my review of that section earlier. I see no reason to have this is 2 places and actually I think that neither is the correct place but rather in Sec. 2.2 or 2.3. But in any case l. 26 should read Fort McHenry Tunnel (not the Baltimore Harbor Tunnel). And line 27 should read Desert Research Institute (not Laboratory). Also, though dioxins and furans (not mentioned here) are emitted from Diesels, these measurements indicate that it is only 0.28 ± 0.13 ng of TEQ equivalent per vehicle-mi, which may be worth adding.

p. 12-30, ll. 33 ff: This really sounds like a very big stretch, in view of your estimate of 60 ng TEQ from trucks vs. U.S. emissions from all sources of 3000 ng. I would stop the paragraph after the word source on p. 12-30, l. 33.

p. 12-30, l. 31: Since we are now in May, what do you want to do about the April 1998 date?

p. 12-32, l. 9-11: I do not agree with the wording which indicates that after aging you don't have to worry about diesel exhaust as much because it is diluted and has been transformed into compounds of less activity. In the first place, however dilute, people are exposed all the time to aged diesel exhaust and not just near the roadway. Second, some of these compounds may be more active than what you started with as you acknowledge on p. 2-56, l. 5-6 and on p. 2-58, l. 29. Thus, as Chapter 2 points out and as I have pointed out in my review, you get a whole set of different compounds such as 2-nitropyrene (not found in fresh exhaust) instead of the 1-nitropyrene found in fresh exhaust. The two are about comparable in mutagenic activity.

p. 12-33, l. 2-3: This statement is not necessarily true since we are talking here about black smoke which derives most of its effect from absorption. The absorption cross section, unlike scattering, is essentially particle size independent. So that seeing smoke or soot says nothing about the size of the particles.

p. 12-33, ll. 26-27: Where did the onset of a common cold come from? I never in the whole document saw any comparison to the effects of episodic DE exposure to the onset of a common cold.

p. 12-34, l. 16: Where did the number 19 come from? I never saw it in the carcinogenicity discussion. This is supposed to be a summary, not a place to introduce new material - without a reference (!)

p. 12-34, ll. 28-29: I have no idea what this refers to. Where in the document is there any support for this? Again, this is not the place to be bringing in further information. This should be expanded and moved somewhere else.

p. 12-35, ll. 17-19: "EPA takes the position..." I have a very strong objection to this wording. This document is not the place for EPA to be taking a position on this or any other matter. The document is a place where the science bearing on a given question is pulled together. I think I can agree with a conclusion but not offered as a position. This document is not the place for position-taking.

p. 12-35, ll. 22-26: This is pure speculation, has not been discussed anywhere in the document. The sentence should be dropped.

p. 12-36; p. 29-30: Could the risk be, say, zero? If so, or whatever lower-bound risk there is, it should be stated. I still do not understand when you get to p. 12-37, l. 23 you cannot give the centroid of the risk and a $\pm \sigma$ and be done with it.

p. 12-37, l. 22: Are we being consistent in upper/lower between here and p. 11-23, l. 22 which we had decided should be lower-bound.

p. 12-37, ll. 30-33: I thought that the gap in the particle deposition spectrum was below 1 μm, in which case I am not sure diesel exhaust will necessarily deposit deeper in the lung (however, I am not sure of this). But the statement about their small size does not give half of the story because these particles are assemblages of small spheres; see the comment above on p. 5-86, l. 34.

p. 12-37, ll. 30-33: In any case you don't know that because you don't know what properties are responsible for the alleged effect of small particles.

p. 12-38, l. 1-4: It should be emphasized that most engine modification steps to reduce NO_X increase the particulate emission rate and vice versa. A more appropriate place for this is Sec. 2.2, as mentioned in the Chapter 2 review.

p. 12-38, l. 7-8: "These special population subgroups are difficult to enumerate, but they do exist." This sounds like conjuring spooks. I am sure you are right but it sounds very odd.

From: "Stayner, Leslie T." <lts2@cdc.gov>
To: ROBERT FLAAK <FLAAK.ROBERT@epamail.epa.gov>
Date: 5/21/98 18:55
Subject: RE: Preparation for the May 5-6 Meeting

Dear Robert

Dear Robert:

I am sending this E-mail to formally express my comments on the EPA draft risk assessment on diesel exhaust. I hope it is okay for me to do so using this medium rather than regular mail. Please let know if it is not and I will send you a letter.

I have limited my review primarily to the qualitative and quantitative health analyses, and particularly those concerning the epidemiologic data. I am attaching a WordPerfect document containing detailed comments that I have on the document. I will try to summarize my more general comments that I expressed at our meeting. I have divided my comments into those pertaining to the non-cancer and cancer qualitative and quantitative sections.

Non-Cancer Qualitative Assessment

Overall, this section was well written and I only have a few comments. First, the review should give greater emphasis to the fact that the epidemiologic studies that have been performed were highly unlikely to be able to detect an effect on the respiratory system, since they were cross-sectional studies that only included active workers. It is well recognized that this type of study may lead to a serious bias due to workers with the disease leaving employment.

Second, the review really must discuss the implications of the studies of PM2.5 and PM10 for diesel exhaust. Diesel is a major contributor to PM and thus most likely contributes to the increased mortality and morbidity that has been associated with environmental PM exposures.

Third, the new research on asthma induced by exposure to diesel exhaust is treated unevenly in this document. It seems that this was added to the document at a late stage, and that this is an important issue that needs to be fully evaluated. In some sections, it is not discussed at all. I think it also may be a bit of exaggeration to suggest that diesel exhaust may be responsible for the increasing trend in asthma incidence.

Non-Cancer Quantitative Risk Assessment

The benchmark dose section seems to be totally illogical. This may reflect a lack of clear EPA agency policy on how to apply this procedure to continuous outcomes. Why was a 10% change used as the benchmark for some outcomes (e.g. lung weight) and a 200% change for others (e.g. bronchiolar lavage enzymes)? I like to the think of the benchmark for categorical variables as a replacement for a NOAEL. A 10 or 1 % risk level is essentially the level of risk at which a toxicologic or epidemiologic study is unlikely to detect an effect. However, the same does not hold true for a continuous variable and it is unclear to me how one picks a benchmark in this case.

Regarding the issue of whether or not to use a safety factor of 3 for interspecies variability, I believe that this is justified and that one could possibly even justify a higher factor. I do not believe that we know enough about the differences in sensitivity of the rats versus humans to argue that the rat is more sensitive than the humans. In fact, the epidemiology suggests just the opposite is true! The risk

estimates that we derive from using the human data are generally much higher than those derived using the animal data.

Cancer - Qualitative Review

The description of the strengths and weaknesses of the individual studies is not well written and at time unbalanced. The reader is left with a false impression of which studies are weak and which are strong. The strongest studies by far are the studies or railroad workers and truckers, since these are the populations with the best defined exposures.

The review overemphasizes the importance of smoking in explaining the findings of these studies. Cigarette smoking has been demonstrated by several investigators to be unlikely a large source of bias in occupational studies. Furthermore, in the epidemiologic studies that did control for smoking it was not found to have much effect.

The review also grossly overemphasizes the potential bias related to the use of death certificate information for lung cancer. This is truly a non-issue, since lung cancer is one cause of death that has been found to be generally reliably diagnosed on death certificates. Furthermore, since there is no treatment for lung cancer the difference between using mortality and incidence data is minimal.

Finally, the silence of this document on the issues related to the exposure-response analysis for the Garshick cohort is puzzling. The EPA ought seriously consider the debate between Stan Dawson and Kenny Crump and discuss these issues in the next draft of the document.

Cancer Quantitative Risk Assessment

In general, I liked the approach of presenting risk estimates from many different data sets and analytic methods. I agree that the greatest emphasis should probably be given to the results from using the epidemiologic data, but I would not at this time dismiss the results from using the toxicologic data either.

I realized that there is a problem with the approach that was used by McClellan and by the EPA in this document. This approach uses a slope for the relationship of lung cancer and duration of exposure from the case-control study by Garshick et al. However, the model that this was taken from does include exposures prior to 1959. Thus exposure was underestimated in this model, which would result in an overestimation of risk. I have the following alternative suggestions for future epidemiologic risk analyses:

1) Use the overall relative risk and the range of exposure estimates from the case-control and/or cohort studies by Garshick et al. to compute a slope. This slope of course would need to be adjusted for differences between occupational and environmental exposures.

2) Similarly, use the overall relative risk estimates from the meta-analysis or from other epidemiologic studies to compute a slope.

3) Use the results from the NIOSH truckers study to conduct a risk assessment. Kyle Steenland and I have a paper in press in which he uses this approach to estimate occupational risks.

The only other option I can see is to wait at least five more years until the results from the NIOSH study of diesel exposed miners is completed, or until the study that the Health Effects Institute is initiating is completed. I think clearly that this option is unacceptable from a public health viewpoint.

These are all my thoughts and comments. I hope they are helpful to you and the authors of this document. Thank you for allowing me to participate in this very important scientific review.

Leslie Stayner

<<R-DIES-9.EPA>>

CC: "Stayner, Leslie T." <lts2@cdc.gov>

Specific Comments
Leslie Stayner

- Page 4-1, 1st paragraph, 2nd sentence - The statement that the "tumorigenic response... is the result of pulmonary overloading" is far too strong. The overload mechanism is still just a hypothesis and other mechanisms may play a role as the document discusses in subsequent sections. I would suggest modifying the statement using words such as "may be primarily the result of".

- Page 4-1, 2nd paragraph, 1st sentence - The statement is not entirely true since one of the studies did report an increase in lung tumors among mice exposed to filtered exhaust (Heinrich et al. 1986a).

- Page 4-3, 2nd paragraph, 2nd sentence - although this statement is supported by the toxicologic data, I don't think it can be supported by the epidemiologic studies. Most lung cancers in humans are bronchogenic in origin and its not clear from the studies performed to date if the excess of lung cancer observed are from tumors of the bronchus or alveoli. Based on species differences in lung deposition and clearance one might argue that the greatest dose in humans will be at the bronchii.

- Page 4-16, 2nd paragraph - A recently published doctoral dissertation by Eileen Kuempel which modelled lung clearance rates in coal miners should be included in this discussion. This model revealed nearly complete shutdown of clearance in these miners, and a very different pattern of lung dust accumulation in humans than in rodents.

  The last sentence needs modification. An excess of lung cancer was noted among workers with pneumocionosis in a study reviewed later in this document. Also a recent paper by Dr. Peter Morfeld from Germany appears to indicate an increased risk of lung cancer among German coal miners (see abstract from the last Inhaled Particles Meeting or the 1998 ICOH meeting in Zimbabwe).

- Page 4-19, 2nd paragraph, lines 4-6 - The review shold note that there is evidence than in the role of interstitialization or particles is greater in primates than in rodents. The dissertation by Kuempel (1997) discussed above makes this point for coal dust, and there is I believe also evidence from experimental studies of monkeys.

- Page 4-20, 4th paragraph - macrophages may not be the primary reservoir in primates since interstitialization may be more important as discussed above.

- Section 5 - It seems really odd that this section contains no discussion of the PM 2.5/10 problem. Diesel is a major contributor to PM2.5 and thus the studies of

PM (e.g. the six city studies) are clearly relevant to the discussion of the potential health effects of diesel.

- Page 5-11, lines 33-34 - it seems that several of the studies discussed in this section did attempt to evaluate chronic as well as acute respiratory effects. Thus I am not sure why this statement was made, unless you mean that the studies were too small or inadequate for this purpose (which I would agree with).

- Page 5-17, lines 4-6 - The fact that these studies only included active workers is a major limitation that should be stressed in this review. Workers who develop symptoms or severe respiratory disease are obviously not going to stay in these jobs and thus these studies are likely to have had a substantial "Healthy Worker Survivor Effect". The effect of this is clearly to bias these studies towards not observing an increased risk of respiratory disease, which is likely to explain the negative and inconsistent findings from these studies particularly for pulmonary function and chronic effects.

- Page 5-19, lines 9-11 - The suggestion that DPM may be involved in the rising epidemic of asthma in this country seems to be a big stretch. Have diesel exposures in the general population increased over the last decade or so paralleling the increase in asthma? A better case needs to be made for this statement or else it should be modified or dropped.

- Page 5-30, line 30 -31 - These sentences suggest that the pulmonary function of these monkeys was "increased". Is this a typo and shouldn't it be decreased if this evidence of obstructive lung disease?

- Section 6.2 - The human and primate studies seem not have been used at all in attempting to derive an RFC. Couldn't some attempt have been made to identify NOAELs or LOAELs from these studies?

- Page 6-4, 2nd paragraph, lines 9-10 - The model developed by Yu and Yoon (1982) has some serious limitations and associated uncertainties that need to be discussed in this section. In particular, the human model has not been adequatetly tested and is largely based on scaling parameters from rats to humans.

- Page 6-15, 2nd paragraph - The text says that a uncertainty factor of 1 was used for interspecies variability; however, in the cover letter from Mr. Flaack and in the summary it indicates that an uncertainty factor of 3 was used.

  The justification for choosing an uncertainty factor of 1 is very weak. First of all, while some allowance should be made for the use of a dosimetric model for interspecies scaling, as already mentioned the model that is being currently used is subject to large uncertainties. Furthermore, the argument that primates

may be less sensitive than rats based on the study by Lewis et al. (1989) seems totally unjustified. This study only had 1 exposure level which showed a response. It is unclear how one can based such a statement on this database?

- Page 6-19, Table 6-2 - What is the basis for the different benchmark definitions used for these different endpoints? How can you justify using a 10% benchmark for some outcomes and a 200% benchmark for others? The whole approach used here for these continuous outcomes is confusing. What is the objective here? Is this an attempt to identify a NOAEL with modeling? If so I am not sure that this is the right way to go about this. If this is the objective then perhaps the benchmark should be set a level corresponding to a level at which the study was unlikely to have the statistical power to detect an effect.

- Page 7-25, line 19-20 - This sentence is illogical. How can a single monkey demonstrate a significant lung tumor response? Do you mean that overall there was no significant increase in lung tumors among this group of monkeys relative to controls?

- Page 8-1, 1st paragraph - Similar statements were made in previous sections. Thus I would suggest dropping this paragraph since it is redundant.

- Page 8-4 - The issue of exposure to coal dust is brought up as a potential confounder of the study by Waller et al. (1981). The review rightly points out that coal dust is not generally believed to be a lung carcinogen, which makes this issue moot. However, isn't the issue exposure to combustion products of coal rather than to coal dust exposure itself? This may be a more complex issue since combustion of coal has been associated with lung cancer in some studies as this document discusses at a later point.

- Page 8-5, lines 4-5 - The document here and in several other places overemphasizes the possibility of disease misclassification due to the reliance on death certificates. For lung cancer this is truly a non-issue, since studies comparing death certificate information to pathologic studies have demonstrated a high degree of concordance.

- Page 8-6, lines 5-6 and 15-16 - These 2 sentences are redundant. Furthermore, the document overemphasizes the potential role smoking might have played in these studies. First of all, it should be made clear that smoking is only a **potential** confounder and in fact several authors (ie. Axelson, Siemyatiki) have demonstrated that it is a best a weak confounder in occupational studies. It should also be noted that in several studies where smoking was controlled for (i.e., Steenland and Garshick) it did not change the findings.

- Page 8-7, lines 7-8 - I suggest changing "confirmed the" to "is consistent" with

the healthy worker effect. One can't really confirm whether there is a healthy worker effect or not.

- Page 8-9, 20-22 - Again this review overemphasizes potential confounding by smoking. The fact that the vital status of 1,765 (5%) of the cohort was unknown is a trivial issue that is not worth mentioning. This is a very small percentage, which is typical of studies of this type. The impact of this would be inconsequential regardless of how the person-years are handled.

- Page 8-9, lines 28-34 - What were the results from this smoking survey that is discussed in this paragraph?

- Page 9-11, lines 2-3 - This last sentence should be dropped. The fact that asbestos and smoking were not controlled for is irrelevant for this negative study.

- Page 8-12, lines 32-33 - Again, death certificate information is fine for lung cancer.

- Page 8-14, lines 1-2 - You should mention that the time dimension for the Cox model was time since first entry into the cohort, and that the model controlled for birth year and calendar time. This is important since it turns out that if you model using age as the time dimension, you do not see an exposure-response relationship.

- Page 8-14, lines 32-25 - In discussing the exposure-response analysis it should be noted that the investigators only included exposure after 1959 and that the duration of exposure to diesel prior to that time was unknown.

- Page 8-15 lines 7-9 - This sentence may be dropped, since it was already stated on the previous page (lines 29-31).

- Page 8-15, lines 24-25 - change may have been to was.

- Page 8-15, lines 29-30 - This study did in fact examine the effect of years of exposure; however, this analysis did include years of exposure prior to 1959.

- Page 8-15, line 33-34 - The word demonstrate is too strong, I would change this to suggest. Also I would change risk to relative risk. A relative risk of 1.5 for lung cancer is actually a large risk on an absolute scale (about 2%).

- Page 8-15 - This review should at least mention the problems with underascertainment in deaths after 1976 in this cohort, that were discovered by K. Crump and acknowledged by the authors of the Garshick study. It should also at least briefly discuss the controversy over whether there is or isn't an

exposure-response relationship in this study.

- Page 8-17, lines 26-30 - This is not an overstatement and in fact is probably an understatement. Axelson has shown that, in general, confounding by smoking could only cause a relative risk of 1.5 for lung cancer.

- Page 8-18, lines 29-30 - Add the word "potentially" before confound.

- Page 8-22 - I would think this might be considered a "hypothesis generating" study, which would not meet the criteria for inclusion in this review.

- Page 8-23, line 15 - The review of this study should note that the greatest limitation of this study was its lack of information on whether or not individuals were actually exposed to diesel exhaust.

- Page 8-25, line 13 - add the word cell to after the word small.

- Page 8-31, line 22 - Change relative risk to odds ratio.

- Page 8-31, line 35 - Put the word significant before excess.

- Page 8-26, line 14 - A reference needs to be added to support this statement. I would think that the use of surrogates for interviews could bias the results either way.

- Page 8-28, line 33 - Actually the transition from steam to diesel engines began in the 1940's.

- Page 8-30, line 11 - Change relative odds to odds ratio

- Page 8-33,line 29 - Change cancers to carcinogens.

- Page 8-35, lines 15-21 - This paragraph makes this study sound very weak. In fact, this is one of the best studies that have been performed. The strengths of this study need to be emphasized, including: the measurements of exposures, the availability of smoking data. I don't think you can say that the limitations of this study resulted in an underestimation of risk.

- Page 8-49, lines 3-4 - The fact that this study demonstrates the utility of city directories would seem to be irrelevant to this review.

- Page 8-59, lines 34-35 - There is a very recently released study of German miners exposed to diesel exhaust that observed a 2 fold excess of lung cancer.

- Page 8-60, lines 9-13 - NIOSH and NCI have in fact been able to identify a

cohort of miners exposed to diesel exhaust with virtually no exposure to diesel exhaust. The latency period (length of followup) of this cohort is not too short to study at this time.

- Page 8-63, lines 10-11. Why is it interesting to note this here? Everyone knows this already.

- Page 8-67, lines 2-3 -You should note here that the studies that control for smoking had little effect in the studies did have information on smoking.

- Page 8-67, lines 21-22 - The study by Steenland was not a study of railroad workers as implied by this sentence. Modify the sentence by adding "and truckers" after railroad workers.

- Page 10-4, lines 35-36 - It is incorrect to suggest that epidemiologic data do not support a mutagenic effect. In fact, the fact that an excess of lung cancer has been observed in studies of working population who are not exposed to high enough levels to induce overload of the lungs would provide indirect evidence that mutations may be involved.

- Page 11-2, line 2 - Substitute "control for" for "eliminate most". One can really never eliminate the potential for confounding.

- Page 11-7, line 22-23 - It should be noted that these potency estimates are for occupational exposures and not for environmental exposures. I suspect this is also true of several of the other potency estimates cited.

- Page 11-7, lines 29-32 - Hattis et al. presented separate risk estimates for smokers and non-smokers.

- Page 11-10, lines 9-10. Again, one can not "eliminate" confounding in epidemiologic studies. It is only possible to attempt to control for it.

- Page 11-10, lines 27-31 - It seems that this document should more directly discuss the issues in the debate between Dawson and Crump on the exposure-response analysis, and if possible offer insight into this issue.

- Page 11-11 - Substitute unit risk for mortality.

- Page 11-11, 2nd paragraph - The possibility of the bladder as a target site should be at least discussed based on the epidemiologic studies that were reviewed in this document.

- Page 11-11, last paragraph - This paragraph suggests that the primary site is assumed to be the alveoli. This would be an appropriate assumption for rats,

but it is not as obvious for humans. Most human lung cancers arise from bronchii and not the alveoli. At least some discussion of this seems warranted.

- Page 11-17, lines 2-3 - How is the fact that the upper bound estimate using this approach being greater than the unit risks derived from the complete animal bioassays a disadvantage? I wouldn't think that the unit risks derived from the complete animal bioassays should be regarded as the gold standard.

- Page 11-17, lines 14-15 - How can you estimate an upper bound when you can't derive one? This needs some further explanation.

- Page 11-20, line 2 - There is also a recent study of German coal miners in which an excess of lung cancer has been observed (P. Morfeld).

- Page 11-21, line 19 - How do we know that this approach yields reasonably good estimates of risk? We don't know what the true risk is so I can't see how one can establish whether or not the risk estimates are "good".

- Page 12-6, lines 20-35 - The issue of PM and its implications for diesel should be more thoroughly discussed in this document.

- Page 12-9, last line - The summary should note the association between bladder cancer and diesel exposure that has been noted in several epidemiologic studies.

- Page 12-11, lines 1-4 - Suggest replacing "showing the trend" with summarizing. This sentence raises an important alternative method for exposure-response analysis, which is to use the meta-analysis results rather than individual studies. I think this is a useful approach, and that it should be used in future drafts of this document.

Comments on Chapter 12

Ron Wyzga

page 12-1, lines 19-23: This is misleading. The mouse studies are not convincing, and the rat studies are controversial with respect to interpretation. On the other hand, diesel emissions contain known carcinogens.

page 12-2, lines 19-26: This presents a very important point which is lost in much of the remainder of the report.

page 12-3, line 31: at high doses; perhaps the exposure levels should be given to provide context.

page 12-10, lines 16-18: Should it mentioned that an independent analyses of these data reached alternative conclusions.

page 12-12: It is important to note that diesel exhaust does contain known carcinogens.

pages 12-16-7: This was discussed in other sections at the meeting. In general I do not support an interspecies factor of 3; EPA Staff said that this was not used, but rather a "data base" adequacy factor of 3 was used in this calculation. First of all, the language and description must be clarified. I'm ambiguous about the latter factor and suggest EPA provide a range for the RfC based upon the inclusion and non-inclusion of this factor yielding a range of 5-15 ug/m3. The monkey study cited was never carefully reviewed in the chapter; hence I am uncomfortable with its use here as supportive to the argument made. If I understood EPA staff correctly, use of these data would lead to a lower value for the RfC. I am disturbed, however, that an essentially negative 2-year study in monkeys at 2000ug/m3 leads to an RfC of 1 ug/m3.

page 12-17, line 17: 1-year average

page 12-21: I was among those who expressed concern about using the human data to derive dose-response. In particular, analyses of the retrospective cohort study data, based on the same population, showed conflicting results depending upon the analysis undertaken. This suggest to me that the range of estimates is greater than that indicated by the document.

page 12-22: I don't like the use of the term biomarker for B(a)P, but calculations based upon a component of diesel exhaust are meritorious as lower limits of risk; in such cases, however, the calculation of risk from B(a)P data should be reviewed carefully. It is my understanding that no committee of EPA's SAB has ever reviewed the basis for the B(a)P risk estimates. If that is the case, it should be noted that the estimates here are not based upon EPA's estimates.

page 12-23, lines 26-32: I am deeply troubled by this analysis. If I understand correctly, the analysis is based upon a net increase of one tumor in a population of several hundred rats. If data from other rat studies had been included, the result would have been negative. So would have the results from an analysis of mouse data. I believe this calculation should be removed from the report.

page 12-25, lines 1-29: I have severe problems with this section and approach. First of all, the risk calculation here is not in accordance with EPA guidelines. Secondly, choice of an alternative endpoint or of response at an alternative dose level would have lead to very different results. If this section is to be retained, sensitivity analyses must be undertaken to demonstrate whether the results are robust.

page 12-27: lines 22-34: Much of this speculative and should be denoted as such or be deleted.

page 12-31, lines 6-17: very well stated

section 12.5 pages 12-31 - 12-38: I applaud these efforts.

Comments on Chapter 8

This chapter provides a fair summary of the recent and most relevant epidemiology literature. It is very similar to the earlier version of the document. Relatively few new studies are presented; these appear to be fairly summarized and critiqued.

There are places in the chapter where better articulation could aid the reader; for example, on page 8-14, middle paragraph, from the description of the Garshick et al study results, it is not clear whether the relative risks presented are for total neoplasms or for neoplasms of the lung. In other cases, particularly in the discussion of bladder cancer studies, more discussion could have been given to the presence of potential confounders Dietary and chemical exposures could be very important for these cancers.

One issue that is dismissed very readily in this document, but covered in more detail in the earlier version, are the analyses of the Garshick et al. study by Crump et al. for EPA and by Dawson for CaliforniaEPA. The current document limits the discussion of these to less than 10 lines on page 11-10, concluding that "Until they [the differences in the Crump et al. and Dawson analyses] are resolved, utilization of the Garshick et al. (1988) study to quantitate cancer risk from DE is not anticipated." It is disappointing that the Agency has not been able to resolve these differences in the past three years. As a minimum these differences should be discussed in some detail in the document so that this panel can determine whether it agrees with the document's conclusion.

The key issue is how to summarize and weight the epidemiology evidence. The document walks a fine line here, and probably ends up making the correct call of "limited" epidemioloic evidence for carcinogenicity, but in its discussion there are several factors that need to be highlighted. As the document points out, because of necessity all of the epidemiology studies are based upon occupationally-exposed individuals; hence there are difficulties in extrapolating results. The document discusses the issue of the "healthy worker" effect. the document also notes that occupational exposures are significantly higher than would be expected in the general population. The magnitude of this difference need be presented and discussed. There is little discussion about how the nature of diesel emissions has changed over time (and geographically as well). Are studies based upon exposures twenty or more years ago relevant for contemporary exposures? I would like to see some discussion of this in the text. The document also discusses the possibility of confounders in an occupational study with emphasis on concurrent asbestos exposure or on smoking. Other lifestyle factors (e.g., alcohol, itinerancy) could also influence the results for the workers generally studied here.

Comments on Chapter 11

I think this chapter and the classification of diesel particulate matter may end up in the right place, but I have problems with the logic and would change some of the discussion. Personally I am more troubled by risk estimates derived from the animal research than by the epidemiology. That fact that positive tumor results essentially exist only for the rat in a situation associated with particle overload troubles me. I would like to listen to what my colleagues have to say about how to interpret the results of the animal data before giving a final decision on interpretation and on the content of this chapter as well as on the merits of deriving quantitative risk assessment estimates from these data.

I have some specific comments about some of the content of the chapter:
pages 11-4 - 11-7: I am not a fan of comparative potency estimates. I find them to be interesting academic exercises, but hold little stock in their results because rankings are rarely preserved for different toxic endpoints. If the endpoint were a definitive one, e.g., tumors, I would be more comfortable, but even then we would lose a lot of information associated with different responses for alternative exposures. For that reason, I cannot assign equal degrees of reasonableness and credibility to this method as to the others. The credibility of this method is further undermined by the fact that the process somehow converts a negative result (for the Caterpillar engine) to a positive risk; how this is accomplished is unclear, but alternative reasonable methods could have resulted in different results.

page 11-7: I would like to learn the reactions of the animal toxicology experts on the panel before commenting upon the assessments based on lung tumor induction data for rats. The Hattis and Silver model could be particularly interesting because it purports to incorporate lung burden.

pages 11-8 - 11-10: I am more comfortable using the epidemiology data with all of their uncertainties than the animal data, but again there are several problems which cause me to hesitate advocating that the risk results be published in this document. First of all, the exposure data are poor and considerable assumptions need be made in order to derive estimates. Secondly I am deeply troubled by the non-resolution of the Crump et al. and Dawson analyses of the Garshick et al. data. It is imperative that this contrast be resolved because, in the absence of any resolution if one gives equal weights to both studies, the range in risk estimates goes from essentially zero to a significant risk level. If the uncertainty is genuine, it need be reflected in the document; if it is not, we need to learn that. The current document provides a disservice by not elaborating upon these analyses and, if possible, deriving conclusions about their relative strengths.

pages 11-11 - 11-16: Again I would like to learn more from my colleagues before making any final judgment about using the rat bioassay data to derive risk estimates. I applaud the efforts by Chen and Oberdorster; this model appears to respond to concerns about the effects of particulate overloading, but it requires subjective judgment about the threshold levels at which particle effects occur. It would be useful to poll several experts about the parameter inputs and to see how the model performs under these assumptions. Using only data associated with low exposures in animal studies is one way to address the particle overload problem, but none of the responses at these levels reflected statistically significant increases in tumors over background levels. The total difference in tumors was minimal; indeed if one had undertaken a similar analysis for the mouse data, it would have suggested a beneficial effect of diesel particulate matter.

page 11-17: I am intrigued by the results of the Pike and Henderson using B[a]P as a surrogate for diesel emissions. These results could be interpreted to explain a fair amount of the carcinogenicity associated with diesel emissions. The document should discuss this issue further and speculate upon the incremental benefits of restricting exposure to diesel emissions beyond restricting exposure to B[a]P. In other words, is a risk management strategy which focuses upon B[a]P adequate to protect the public from diesel emissions?

pages 11-17 - 11-22: A good discussion, which could be augmented given some of my above comments. The discussion need emphasize the facts that all diesel emissions are not the same in characterization as well as in concentration. Anything that can be said about these changes over time would be particularly useful here. This could aid in the interpretation of various studies and analyses as well

pages 11-22 - 11-23: Changes made in response to the above should be incorporated here.

OTHER

I have reviewed the EPA responses to earlier CASAC comments and some concerns about the response to **Comment 6**: The noncancer concerns for which the RfC was based were those associated with chronic exposures. In my opinion it is not appropriate to adjust this RfC because of allergic hypersensitivity. That argument would be relevant for an RfC based upon acute exposures and responses.

Comment 9: Haber's law is exercised over a considerable range of exposures and times in the document. I believe that it is incumbent upon the authors of the report to demonstrate that Haber's law is relevant for the full range of dose -exposure time periods for which it is applied. This is of particular

concern when results are presented across experiments with very different exposure protocols. For example, Table 5-2 presents C x T data without qualification for exposure periods varying from 19 weeks to 3 hours (a factor of 600), and concentrations ranging from 0.21 to 6.8mg/m3 (a factor of 30); other tables are similar. As a minimum I would like to see a footnote addressing this concern in the various tables.

Ronald E. Wyzga, Sc. D.
May 1, 1998

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