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

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Sections of the document, and especially the description of diesel engine emissions, are considerably out of date.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 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 Emission, 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

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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).

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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)