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Discussion Paper for CASAC–Diesel Health Assessment Issues

Prepared for the June 10, 1999, meeting of the U.S. Environmental Protection Agency's Clean Air Scientific Advisory Committee at Research Triangle Park, North Carolina. The Committee will be consulting on this discussion paper.

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PREFACE

In October 1998, the U.S. EPA's Clean Air Scientific Advisory Committee (CASAC) provided peer review comments on a draft Health Assessment Document for Diesel Emissions (EPA/600/8-90/057C, February 1998). The U.S. EPA's National Center for Environmental Assessment requested a consultation with CASAC to discuss the ongoing risk assessment approach for addressing the major CASAC comments. The contents of this discussion paper are draft, "do not cite or quote" in all respects and should not be interpreted to be final risk assessment conclusions or Agency policy. A fully revised Diesel Health Assessment Document is expected to be available for peer review and public comment in October 1999.

Introduction

The National Center for Environmental Assessment (NCEA), the risk assessment office in ORD, has been engaged in preparing a Health Hazard Assessment for Diesel Engine Exhaust (hereafter "Assessment") for a number of years. Recent history of that endeavor involves a February 1998 draft Assessment (U.S. EPA, 1998) which was reviewed by CASAC in May 1998 with follow-up written comments in October 1998. As the completion of the Assessment is very important to EPA's Office of Mobile Sources, NCEA is attempting to move ahead toward completion of the Assessment and a final CASAC review in the Fall of 1999. Given the importance of completing this Assessment in a timely manner, a consultation with the Committee to discuss NCEA's approach for addressing the key CASAC issues was desirable.

1998 Draft Assessment Overview
Key CASAC Comments
Current Approach in the Context of Preliminary Findings

The information to follow captures the major CASAC comments and outlines the current NCEA approach to revising the 1998 Assessment, taking account of the comments. This is done in the context of some preliminary Assessment findings so that the impact of the CASAC comments and the NCEA approach can be considered in a relevant context.

What is the Purpose of the Assessment and How is it Constructed to Serve the Purpose

The Assessment is a compilation of key information that would establish the toxicity factors pertinent to describing how exposure to diesel exhaust might affect human health. This type of health assessment document develops answers and conclusions for two questions: (1) how likely the agent is to pose a hazard to human health (Hazard Characterization), and (2) what dose-response relationships can be applied to best determine the possible magnitude of the hazard for populations (Dose-Response Characterization). A population exposure assessment is not included in this Assessment nor is a full risk assessment. As is typically the case for Air Program assessments, the regulatory program (i.e., OAR-OMS) will develop the exposure assessment, and actually combine the toxicity information and exposure information to create the full risk assessment, if such is needed for regulatory purposes. Health Assessment Documents are generally less encyclopedic than Ambient Air Quality Criteria Documents, and they typically use some different procedures to interpret certain types of health effects, e.g., use of a Reference Concentration (RfC) derivation for noncancer effects.

The Assessment has a series of chapters which review discrete topics and develop a summary of that topic as well as noting key interfaces with other chapters. A hazard and dose-response characterization chapter then integrates certain key information to develop the overall scientific rationale in support of findings

about the hazards and related dose response, key uncertainties, important inferences drawn and assumptions made, etc. This Chapter contains the bottom-line findings of the health assessment.

Cancer Health Hazard

In the 1998 Assessment NCEA laid out the human, animal, and supporting toxicological data and concluded that environmental exposure to diesel exhaust posed a "Probable" (weight-of-evidence Category B-1) inhalation carcinogenicity hazard to humans. This was based on positive epidemiology evidence from occupational studies, sufficient evidence of animal carcinogenicity in long-term bioassays at high doses, and several types of supporting evidence such as mutagenicity and analytical data demonstrating the presence of many suspected and some known carcinogens in the diesel mixture of gases and particles. With no clear available evidence to infer a lack of cancer hazard at typical environmental levels of exposure, inference was also made that the hazard potential exists at low exposure levels, not just at higher exposures, albeit the magnitude of the dose response at lower levels (outside the range of observation in the epidemiologic studies) is still somewhat uncertain. The weight-of-evidence conclusion was based on guidance contained in EPA's 1986 Guidelines for Carcinogen Risk Assessment. Although not specifically called for in the 1986 guidance, NCEA restricted this hazard finding to the inhalation route of exposure. This approach of specifying route is consistent with the evolving risk assessment guidance proposed by EPA in 1996. NCEA also noted that using EPA's 1996 Proposed Guidelines for Carcinogen Risk Assessment, the weight-of-evidence characterization for a human cancer hazard for an inhaled diesel mixture would contain the statement that it was "very likely" that a human carcinogenic health hazard exists, and that this statement becomes more certain as one approaches levels of exposure experienced in the epidemiologic studies described in the assessment.

<u>CASAC Comment:</u>

- The CASAC was in general agreement that there is limited evidence for a causal association between occupational exposure and lung cancer.

- The panel noted that the discussion of threshold versus nonthreshold needed strengthening.

<u>NCEA Approach:</u> We will refine our discussion of the weight-of-evidence classification for cancer hazard. The respective roles of the epidemiologic data, animal toxicology, and information relating to mechanism(s) of carcinogenic action will be carefully articulated. We will respond to CASAC comments by being more clear about the possible species-specific response in the rat as well as the high exposure, particle overload issue. The Assessment will be improved by enhancing and better integrating discussions regarding possible mode(s)-of-action (MoA), the latter would also bring in the question of threshold versus nonthreshold dose response. We will more fully elucidate the basis for inferring a low-dose hazard from

the higher occupational exposure-response database, considering both the quantity and quality of current environmental exposure to diesel.

Cancer Slope Factor and Unit Cancer Risk

In 1998 NCEA proposed the combined use of several different data sets to define a range of unit risk estimates pertinent to environmental levels of exposure. The different data sets (i.e., rat bioassay response data, indirect comparative risk derivation approaches based on dose-response of other airborne particulate pollutants compared to diesel constituents, for example BaP and coke oven emissions, and epidemiology based estimates from the Garshick et al. (1987) railroad work case-control study) were given equal weight in defining the low and high end of a range of plausible unit risk estimates; the range was 1E-5 to 200 E-5 per $\mu g/m^3$ of diesel particulates with the animal based estimates defining the lowest end of the range and the occupational railroad worker study defining the higher estimates of unit risk.

CASAC Comments:

- The 1998 Assessment's approach, using rat lung tumor data to develop lung cancer unit risk estimates for low level exposures, is not supported by present knowledge of the nature and likely mechanisms of the rat response.

- The use of the McClellan risk model of the Garshick railroad worker case-control study was not appropriate without additional analysis or data.

- The epidemiology database may be the best to consider for quantitative risk derivation, though considerable uncertainty remains regarding the most appropriate use of the Garshick data.

- The utility of adopting indirect-comparative risk-based estimates was discussed but no consensus was achieved regarding this approach.

- The 1998 Assessment falls short in its analysis of the exposure-response relationships which are crucial for extrapolating from occupational to environmental levels.

- The bioavailability of particle organics in the human lung needs more discussion since it has a bearing on supporting certain dose response and risk extrapolation approaches, including the preference for nonthreshold versus threshold dose response.

NCEA Approach: NCEA has dropped the rat based estimates, recognizing the controversial nature of the target cell hypothesis and the mechanistic considerations in the rat vis-a-vis potential human response. In addition, the high doses administered to the rats make the response in this species difficult to relate to lower human environmental exposures. While the indirect-comparative risk approach will be discussed, it is one step removed from a direct basis for risk estimation and would not be favored over a suitable epidemiology-based unit risk derivation. In this regard, NCEA agrees with the CASAC advice that using epidemiology data to determine a unit risk estimate is preferred at the present time. Additional attention also will be given to discussing MOA including bioavailability of organics. While the application of the unit risk estimates derived from occupational studies to low-level, ambient exposures remains uncertain, NCEA continues to maintain that the unit risk estimate has applicability to such exposures. Given that some estimated ambient exposures overlap with the low end of the exposures in the Steenland et al. study (1998), use of the unit risk as a slope factor for estimating ambient risk is considered to be appropriate. NCEA recognizes that this inference becomes increasingly uncertain as the unit risk is applied to smaller and smaller incremental exposures which are far below the range of observation that was the basis for their derivation. There is currently no reliable data upon which to base application of a threshold model. However, this alternative approach will be discussed in the final document.

While the Garshick railroad worker studies will be used to support the hazard weight of evidence, NCEA will not attempt to reconcile the dose-response debate associated with the Garshick et al.(1988) cohort study (i.e., is there a dose response suitable for risk derivation?). Railroad worker cohort data from Garshick has been evaluated for dose-response by two parties, an independent consultant and by the California EPA (Cal EPA), with different conclusions. The consultant's analysis showed no discernable dose-response, while Cal EPA modified the exposure assumptions, adjusted the eligible cohort and showed a dose-response. The Garshick et al. (1988) cohort study is currently being updated to improve an undercount of mortality in the last few years of follow-up.

The 1998 Assessment's use of a simplistic approach to derive a potency estimate from the Garshick et al. (1987) case-control study as developed by McClellan et al. (1989) was not favored by CASAC without additional analysis and data adjustment. While some CASAC members believed that we should try to reconcile the railroad cohort and case control study dose-response issues, the new Steenland et al. (1998) study and ongoing endeavors to generate additional railroad worker data suggest to NCEA that it may be unproductive to engage in more dose-response analyses of the Garshick cohort study at this time.

After the 1998 Assessment and CASAC review, an updated publication, Steenland et al. (1998), became available which laid out a new risk assessment based on a new retrospective exposure evaluation for the earlier Steenland et al. (1990) case-control study. Steenland et al. (1998) indicated significant positive

trends (i.e., as much as 1.69 in the highest exposed group) in exposure-response between cumulative diesel exposure, as defined by exposure to elemental carbon, and lung cancer risk.

With the Steenland et al. (1998) risk assessment available and recognizing the strengths of the Steenland methods (i.e., robust industrial hygiene study to benchmark exposure as well as reasonable assumptions to estimate past exposure which integrates with the case-control study, sensitivity analysis to several types of exposure variables, controls for possible confounding by smoking and asbestos, and knowledge of when case exposures began), Steenland et al. (1998) is a preferable starting point for EPA to estimate risk for environmental levels of exposure.

Steenland et al. (1998) used logistic regression analysis to fit the data, with and without a 5-year lag, and taking account of individual smoking histories, together with various assumptions about past emissions, and with alternative exposure-response models. Steenland et al. (1998) used a logistic exposure-response model, which with a minor adjustment, can be easily adapted to define unit risk under environmental exposure conditions. This unit risk estimate at the low exposure end of the Steenland et al. (1998) study will be used to define a cancer potency slope. NCEA will use an approach similar to that of Stayner et al. (1998), who estimated risks to coal miners under various exposure concentrations based on minor adjustments to the Steenland exposure-response model. In addition to the difference of using environmental exposure conditions (continuous exposure for a 70-year lifetime,), another difference is that NCEA will adjust for competing risk using the mortality rate for the total U.S. population, instead of using only the mortality rate for white males as did Steenland et al. (1998) and Stayner et al. (1998). NCEA also believes that additional in-depth analysis of the Steenland data and methodology would be useful, although it is not necessary in order to use the study in the current hazard assessment. For example, the lung cancer response could be correlated with intensity of exposure rather than simply cumulative exposure and the control for confounders such as smoking could be re-addressed. NCEA will pursue this further analysis, together with NIOSH, over the next year.

In the meantime, on the basis of the Steenland cumulative exposure estimates and exposure-response model, NCEA will establish a Point of Departure (POD) for extrapolation to lower exposures. The POD is described in the 1996 Proposed Guidelines for Carcinogen Risk Assessment as the lowest reliable dose associated with response within the range of observation of the study under discussion. As a default, based primarily on the power of animal toxicology tests, the POD is frequently described as the 95% lower-confidence limit of the exposure associated with a 10% risk (LED_{10}). Ultimately, if data allow, EPA would like to use the lower bounded LED_{05} or LED_{01} for the POD. It is of interest to note that in the Steenland et al. (1998) study, worker exposures ranged from 19 to 2440 $\mu g/m^3$-years, with a median of 358 and a 95 percentile exposure of 754 $\mu g/m^3$-years of elemental carbon. Transforming this range to

diesel particulate concentration, and accounting for continuous exposure for 70 years, provides an environmental equivalent range for locating a POD. This POD would be close to or overlapping diesel exposure estimates in many U.S. urban areas. (For comparison purposes to Steenland exposures, 6 $\mu g/m^3$ of continuous environmental exposure [24 hour per day for 70 years] to diesel particulates equates to approximately the median occupational exposure in the Steenland study).

Ideally, the shape of the dose extrapolation curve below the range of observation would be dictated by a biologically based dose-response (BBDR) model, reflecting knowledge of the mode of carcinogenic action. Mechanisms of action for diesel carcinogenicity in humans are not at all clear, although several modes of action have been postulated and will be discussed in the Assessment. No BBDR model has yet been developed for the carcinogenic response to diesel exhaust. Given the complex mixture of organics, and their related mutagenic properties, contained in a typical diesel exhaust mixture, a linear extrapolation into the low-dose range is a biologically plausible choice. These data and other considerations support the selection of the linear default for extrapolation below the range of observation. However, extrapolation may not be necessary for the intended purpose of this Health Assessment, considering the overlap of some environmental exposures with those in the Steenland occupational study. On the other hand, threshold hypotheses based on particle effects only and or the lack of bioavailability of particle organics suggest that low-level exposures to humans may not pose a hazard or risk below exposures seen in the occupational studies. NCEA will discuss these threshold hypotheses in the full Assessment. In the absence of more definitive insights, NCEA believes that nonthreshold approaches are the more prudent ones at the present time.

Given that the approximate range of 1990-1995 ambient environmental exposure for some subpopulation groups (i.e., 2-6 $\mu g/m^3$ for all diesel sources with 1-3 $\mu g/m^3$ for highway diesels - OMS preliminary estimates) are likely to overlap with a POD from the Steenland et al. (1998) exposures, the need for extrapolation beyond the range of human data observations is minimal. NCEA will also present the implications of the choices made in the data transformation, the selection of the POD, the use of a straight line to extrapolate to lower exposures, the changing character of diesel emissions over time, and will discuss alternative choices that might significantly effect the outcome of the Assessment. The unit risk derived from this effort would be characterized as a plausible upper bound estimate, recognizing the input data uncertainties and the risk assessment methods and preferences used to derive the estimate. Planned additional analysis over the next year with NIOSH investigators over the next year may be helpful in addressing some of the uncertainty.

Note that the nonlinear default approach articulated in the 1996 Proposed Guidelines for Carcinogen Risk Assessment involves calculation of a Margin of Exposure (MOE) if a nonlinear MoA is supportable and

output from a nonlinear model is not available. The MOE provides the assessor and decision makers with an estimate of how far environmental exposures of interest are from the lower end of the observed range. This is presented as Dose (POD)/ Dose (exposure of interest). With 1990-1995 estimated ambient levels in the 1-6 $\mu g/m^3$ range, they are within the range of occupational exposures (the median Steenland occupational level converted into environmental equivalent levels is about 6 $\mu g/m^3$), and therefore, MOE's would be 1 or less for some portion of the population. Higher diesel exposure microenvironments (e.g., 5-10 $\mu g/m^3$, or higher) would be well into the occupational range. This issue will be discussed further in the Assessment.

Health Hazard Characterization/Effects Other than Cancer - Reference Concentration

For toxic air pollutants, other than criteria air pollutants, hazard and dose-response characterization is accomplished through the derivation of a Reference Concentration (RfC). An RfC is defined as an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to humans (including sensitive subpopulation groups) that is likely to be without appreciable risk of deleterious noncancer health effects during a lifetime. EPA's RfC methodology was used to develop an RfC for diesel exhaust exposure, this included establishing a critical effect and identifying related No Observed Adverse Effect Levels (NOAELs) or Lowest Observed Adverse Effect Levels (LOAELs), estimating human equivalent doses for the animal study based NOAELs/LOAELs, and further lowering the human equivalent doses by two types of uncertainty factors. Uncertainty factors, generally 3- to 10-fold, are intended to account for (1) the variation in sensitivity among members of the human population, (2) the uncertainty in extrapolating laboratory animal data to humans, (3) the uncertainty in extrapolating from data obtained in a study that is of less-than-lifetime exposure, (4) the uncertainty in using LOAEL data rather than NOAEL data, and (5) the inability of any single study to adequately address all possible adverse outcomes.

In the 1998 Assessment NCEA recommended that pulmonary histopathology observed in the rat lung, across several studies and at exposures below particle overload, be selected as the lowest exposure-related indicator of an adverse effect that could be inferred to represent a potential hazard indicator for humans. This was in the absence of adequate epidemiology studies on exposure to diesel exhaust to address noncancer chronic toxicity. These adverse effects were designated the "critical" effects. A critical effect is defined in the EPA RfC methodology as the first adverse effect, or its known precursor, that occurs as the dose rate increases. Following the Agency's approach to setting an inhalation RfC, NOAELs for the critical effects were determined from the rat lung studies and related human equivalent exposures were estimated using a rat-human dosimetry model. For diesel specifically, uncertainties related to intraspecies variability (i.e., sensitive members of the population) were considered by applying a 10-fold uncertainty factor to a human equivalent NOAEL of 155 $\mu g/m^3$ from a rat study, and uncertainties relating to

incomplete knowledge of rat to human interspecies extrapolation were considered by applying a second uncertainty factor of 3. The composite uncertainty factor was 30 (10 × 3). The uncertainty factors applied to the human equivalent NOAEL produced an RfC of 5 $\mu g/m^3$ (155 $\mu g/m^3$ /30 = 5 $\mu g/m^3$) for chronic human exposure.

CASAC Comments:

- A more understandable discussion of the RfC methodology (e.g., including the use of uncertainty factors in general and specifically for diesel) is needed, thereby, allowing a better judgment about the recommended RfC value.

- An expanded discussion of possible linkages between the health effects database for diesel emissions to that for airborne particulate matter (e.g., $PM_{2.5}$) is needed, if a case is to be made for treating exposure to diesel differently from the aggregate environmental PM to which it contributes.

NCEA Approach: Some newer noncancer health effects data will be added to the noncancer database (e.g., exacerbation of immunological responses/allergenic inflammation). These have been reviewed to determine whether they should replace rat lung histopathology as the "critical effect" for setting an RfC. Preliminarily, the use of pulmonary histopathological responses in the rat are reaffirmed as the "critical effect" for the RfC derivation. A clear and concise discussion about the selection of RfC uncertainty factors (i.e., 10 for intra human variability and 3 for interspecies extrapolation) will be added.

Pulmonary histopathological alterations (inflammation and fibrogenesis) observed in rats will remain the "critical" endpoint for the noncancer RfC assessment, given that pulmonary histopathology is shown consistently in several species with clear dose response under long-term controlled exposure scenarios, whereas, allergenic effects are shown consistently in both animal and clinical human studies, but dose response and C × T relationships for the allergenic effects are not yet available under any exposure scenario. The pulmonary histopathology observed in rat studies is used to infer pulmonary effects that may occur in humans, assuming the rat is a satisfactory surrogate model for humans, as well as being representative of an unspecified sensitive response that might occur in humans at doses equivalent to those studied in the rat. Enhanced allergenic effects have been demonstrated in humans but mostly in sensitized individuals that were exposed via nasal instillation to relatively high levels of bolus doses of diesel exhaust. The emergence of this information on enhanced allergenic effects will be noted, but the current lack of sufficient information to quantitatively evaluate this effect will be highlighted. Both endpoints have uncertainties with regard to relevance to humans. These uncertainties will be discussed as will the "public health protective" nature of the RfC.

With the critical effects remaining the same as before, clarifying the choice of uncertainty factors will be a priority. No compelling rationale exists for applying any additional uncertainty factors (i.e., 10 for intra-human variability and 3 for interspecies extrapolation = 30) beyond the two already recommended. The critical database for this compound is extensive with several excellent long-term rat studies; animal NOAEL's can be identified, and animal to human extrapolation is enhanced by using a rat to human dosimetry model to account for deposition and retention. The use of an uncertainty factor of 10 for sensitive subpopulations is standard unless there is evidence to suggest that either a smaller or larger uncertainty factor is warranted. The choice of a factor of 3 for interspecies extrapolation is consistent with the Agency's RfC methodology, noting that the 3 for interspecies uncertainty factor of 3 is a science policy preference when a dosimetry model is used and the uncertainty could have been as high as 10 without the dosimetry.

A critical and comparative evaluation of available models of diesel particulate (DP) particle deposition/clearance will also be added. The rat overload topic also will be presented in this context and its relevancy to diesel particulate noncancer health risks will be critically evaluated. A 5 $\mu g/m^3$ RfC recommendation is likely to be reaffirmed. We would also note that persons exposed to PM levels higher than this may be at increased risk for increased pulmonary morbidity and mortality, in accordance with reported $PM_{2.5}$ effects, and perhaps, enhanced-allergenic effects.

CASAC encouraged a better discussion linking the effects and risk assessment findings for exposure to diesel exhaust (RfC of 5 $\mu g/m^3$ is proposed) to those associated with the $PM_{2.5}$ ($PM_{2.5}$ annual average standard is 15 $\mu g/m^3$). We will better link these topics in the Assessment chapters on dosimetry and noncancer effects. As far as impact of the similarities or distinctions for the Assessment conclusions, we will mention for example, the implications of the following: number of fine particles is greater with diesel compared with most ambient PM; the mean diameter of particles is smaller with diesel; the amount of organics present with diesel is much greater; and note that these diesel characteristics can be diluted when mixed with other ambient PM. These circumstances give the impression that a pure diesel exposure could potentially be more toxic than the same mass of typical ambient PM exposure that had only small or minor quantities of diluted diesel PM; this impression may or may not be an absolute. A direct comparison of the RfC value to the $PM_{2.5}$ criteria is a bit more problematic. There are different risk assessing methodologic approaches being employed as well as a slightly different risk assessment goal to be achieved. With the $PM_{2.5}$ criteria, the Agency has sought to protect sensitive people using LOAELs from human studies. With the RfC we are estimating a level, within perhaps an order of magnitude, without appreciable risk. With diesel there are no adequate human studies for noncancer effects, so animal NOAELs based on a "critical effect" (the most sensitive noncancer adverse response) have been used with

uncertainty factors to account for sensitive members of the population as well as animal to human extrapolation uncertainty, both of these uncertainties are implicitly accounted for in the human PM data.

Particulate matter from any source is the same to a given sampling system, so diesel particles can be part of any measured ambient PM. Typically, ambient PM in most areas is comprised of 50% or more sulfate or nitrate plus crustal materials. The actual make up varies according to local conditions and specific PM emission sources. A minority of the mass of ambient PM is elemental carbon and organics, while these are the majority of diesel PM. Diesel particles have an elemental carbon core which roughly makes up 20%-70% of the particle mass, the carbon core is coated with a wide variety of organics (e.g., alkanes, alkenes, aldehydes, monocyclic aromatics, PAHs). Diesel PM would be most similar in this regard to gasoline vehicle PM, wood smoke, and PM from meat cooking. In any urban area with on road or off-road diesel engine use, some of the ambient PM is certainly diesel. OMS estimates that on an annual average basis diesel PM is around 1-6$\mu g/m^3$ excluding obvious situations that would have much higher than normal levels such as downtown bus stops and locations adjacent to high volume truck routes. Diesel PM at a 1-3 ug/m^3 level is estimated to constitute about 5%-10% of a typical annual average $PM_{2.5}$.

These issues and others will be discussed in the final Health Assessment and ultimately in OMS' characterizations of ambient exposures to diesel particulate matter

EMISSIONS, Past and Present, and Implications for Risk Assessment

In the 1998 draft Assessment NCEA had a chapter which over viewed the history of emissions in terms of physical chemical characteristics, patterns and trends of emission changes over the years, some discussion of transformation and fate of emissions in the atmosphere, and some scant information on exposure. A concluding Risk Characterization Chapter attempted to integrate these topics into the risk assessment findings, however, the insight gained from the emissions information was limited. A number of issues and uncertainties derive from these topics including, the appropriate dosimeter for diesel toxicity and exposure, the use of toxicity data coming from older engines to define human risk versus the use of that information on newer engine exhaust exposures, and broad ranging questions about estimating population exposure.

<u>CASAC Comments:</u>

- The emission characterization information was outdated.

- The Panel clearly pointed out that there was a critical need to more explicitly consider how changes in emissions over time might influence the nature of their toxicity; to portray the differences between emissions which define current or future risk from those older emissions pertinent to the epidemiology studies and animal toxicity testing; and in the end provide a clear statement about how the differences in emissions affect the value of key data used to characterize hazard and risk to present day exposure estimates.

NCEA Approach: The NCEA approach to these issues will be to redo the chapter on emission characterization with a goal to be more up to date with regard to delineating trends in emission changes over time, and or describing any known factor which would be likely to enhance the understanding or limitations of risk assessment conclusions. We aren't intending to provide an encyclopedic review of all data, but to improve the characterization of those topics which would directly influence the risk assessing questions for the lung cancer, pulmonary histopathology effects, and some aspects of exposure assessment that interface with toxicity. Note that exposure assessment per se is handled by OMS, separate from the development of the Diesel Health Assessment Document.

The question of what is important about emission changes and the composition of emissions/exposure won't be properly answerable until health science has provided a better understanding about the MoA for diesel induced carcinogenicity and the possible histopathologic effects in humans.

The Assessment Chapter dealing with emissions is being revised, to show trends in emission changes to the extent such trends can be discerned. Given the revised assessment strategy to place more emphasis on the epi studies, especially long haul truck drivers, the period of highway diesel engine emission interest is 1949-1982. Steenland et al. 1998 used a 1991 industrial hygiene study to benchmark relevant exposures to 1991 and then Steenland uses Sawyer and Johnson et al.1995 emission data and Federal Highway Administration data on miles driven together with grams/emissions per mile as the scaler for retrospective

exposure. We will see if any additional insights about exposure to the diesel mixture over the 1949-1982

period are evident and how this might compare with highway and other diesels of the more current day vintage.

With $\mu g/m^3$ of DP (diesel particulates) being the currently convenient dosimeter (perhaps a role for $\mu g/m^3$ of elemental carbon too), we have little choice in the interim but to use $\mu g/m^3$ of DP as the common metric between toxicity, and past and present ambient exposure. MoA understanding is also a prerequisite for properly assessing exposure, in the meantime, a default situation exists where $\mu g/m^3$ of 1950-1980's exposure (total particle mass) is assumed to be directly proportional in health consequence to current day $\mu g/m^3$ exposure.

In terms of trends in emission changes, OMS and NCEA preliminarily believe that:

- Possible emissions differences between diesel locomotives and current highway diesel engines are no longer an issue because of our plan to not rely on the locomotive worker study for purposes of quantitative risk assessment.

- Emission differences between the light duty diesel vehicles used in many of the animal exposure studies and current highway diesel engines are also no longer an issue because of our plan not to rely on animal data, in accordance with CASAC's recommendations.

- Thus, the question of exhaust composition is an issue, if at all, only within the highway and nonroad diesel categories. Ideally, compositional issues would be resolved through actual emissions data. However, consistent emissions data are available only for engines produced in about the last 10 to 15 years. There are essentially no data on even the PM mass emission rates, much less on the composition of PM, from highway diesel engines manufactured prior to about 1975, with test and analysis procedures presently considered representative and comparable to procedures used on more modern engines. Starting with engines produced in the 1980's, there is considerable data on PM mass emission rates and limited data on composition. Therefore, it is necessary to infer the composition of PM from earlier engines based on an understanding of the technology evolution of diesel engines.

- While California and federal emissions standards applied to highway diesel engines starting in the

1970's, it was not until around 1990 that emission standards became stringent enough to force major changes in technology. In the period between 1950 and 1990, technology evolved, but not dramatically. Shortly before and after 1990, manufacturers greatly reduced the production of 2-stroke engines and added turbocharging to 4-stroke engines. In the period prior to around 1990, 2-stroke engines had higher PM emission rates and a composition more dominated by unburned engine oil than did 4-stroke engines. PM emission rates after the imposition of emission standards for PM are more similar between 2-stroke and 4-stroke engines. In the period of the trucker cohort's exposure, 2-stroke engines dominated bus applications, but were less present in freight truck applications. Thus, the shift towards more 4-stroke engines had an attenuated effect if any on truck driver exposures.

- Between the pre-1990 to post-1990 (approximately) periods, model year-specific PM mass emission rates have declined by a factor of two to three. Because of the fleet averaging effect, the change in fleet emission rate has been somewhat more gradual and smaller.

- Most diesel engine testing programs have quantified the split between elemental and organic carbon. Organic carbon compounds comprise on average about 20% of the PM mass from pre-1990 (approximately) engines, but individual engines vary. In the 1990's, at least some lower PM engines designed to meet more stringent PM standards have tended to have a smaller emission rate of elemental carbon, and a higher organic fraction in the PM.

- Broad compositional testing of diesel PM for specific organics is rather recent, and limited to a few research centers. It is not possible to completely characterize the composition of diesel PM. Only about 5% of the PM organic mass has typically been identified by molecular species. Even this degree of characterization has been accomplished only on engines sold since about 1985. EPA will examine this data closely in preparing the next draft of the diesel health assessment document. Our review so far suggests that at least among 4-stroke diesels engines, there seems to be no specific evidence that since 1985 any potentially toxicologically significant organic compounds have decreased or increased out of proportion to the change in organic mass. In particular, most PAH emissions, particle phase and gaseous phase, show a declining trend in mass emissions from 1984-1993, while the PAH and nitro-PAH composition of emissions have not changed significantly

during last 10 years. Projecting backwards, since 4-stroke engine designs changed little prior to around 1990, there seems to be no basis for any out-of-proportion changes as far back as the introduction of highway diesels. We will examine the data further regarding a possible trend within 2-stroke engines as a result of better engine oil consumption control, and regarding the significance of the shift from 2-stroke to 4-stroke engines. While there are little if any data on organic composition of PM from nonroad diesel engines, the lack of evidence for strong organic composition changes over time among highway diesel engines and the similarity in design of highway and nonroad engines suggest that health effects data relating back to highway exposures is relevant to nonroad exposures also.

- Very limited data on engines produced since about 1990 suggest a possible size distribution shift to smaller particles, in addition to the possibility of a higher organic fraction as mentioned above. However, all size distribution findings based on laboratory studies to date are in doubt pending the outcome of research to determine PM sampling methods that are validated to be representative of ambient mixing conditions. With the exhaust catalysts used on a very small portion of engine production in the 1990's, the organic content of the PM is substantially reduced.

- Reduction in the sulfur content of diesel fuel results in lower sulfate emissions. The effect of other possible diesel fuel changes on organic composition has been little explored.

- Emissions which have been in the ambient environment for about 24-48 hours are said to be "aged", fresh exhaust has free radicals; these radicals can induce DNA damage, aged exhaust has fewer free radicals because the particles have been subjected to chemical and physical alterations in the atmosphere, though some alterations may include additional nitrification of plain PAH's. However, it may be that the bulk of population exposure to diesel PM is to particles that have been emitted within 24 hours. If so, then the general population and the trucker cohort may be similarly exposed to free radicals, on a mass proportional basis.

We will endeavor to continue our inquiry into these matters and strive to factor them or others that emerge into our risk characterization, which we have not yet begun to revise.

References

Garshick et al. 1987. A case control study of lung cancer and diesel exhaust exposure in railroad workers. Am Rev Respir Dis 135:1242-1248.

Garshick et al. 1988. A retrospective cohort study of lung cancer and diesel exhaust exposure in railroad workers. Am Rev Respir Dis 137:820-825.

Steenland et al. 1990. Case control study of lung cancer and truck driving in the teamsters union. Am J Public Health 80:670-674.

Steenland et al. 1998. Diesel exhaust and lung cancer in the trucking industry: exposure-response analyses and risk assessment. Am J. Ind Med 34:220-228.

Stayner et al. 1998. Predicted lung cancer risk among miners exposed to diesel exhaust particles. Am J Ind Med 34:207-219.

U.S. EPA. 1998. Health Assessment Document for Diesel Emissions. (Draft) National Center for Environmental Assessment, Washington, DC. EPA/600/8-90/057C.