**RESPONSES BY THE STAFF OF THE
OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT (OEHHA)
TO HEALTH EFFECTS RELATED COMMENTS ON THE
JUNE, 1994, DRAFT TECHNICAL SUPPORT DOCUMENT (TSD)
(INCLUDING PART B, "HEALTH RISK ASSESSMENT FOR DIESEL EXHAUST")
FOR IDENTIFICATION OF DIESEL EXHAUST AS A TOXIC AIR CONTAMINANT
(TAC)**

Table of Contents

Comments of the American Mining Congress

1. Comment summary: The validity of the Garshick et al. (1988) epidemiology data is in question because OEHHA's analysis shows an inverse dose-response relationship. OEHHA bases its diesel exhaust unit risk on the Garshick, et al. (1988) cohort study, but examination of the relative risks for exposed subgroups paradoxically shows higher risks for groups with lower diesel exhaust exposure. Of the exposed subgroups of railroad workers, the shop workers and hostlers were subgroups with the greatest exposure. However, Garshick et al. reported that, with the shop workers excluded, the relative risk actually went up a little rather than down. Therefore, if the OEHHA analysis is applied to the Garshick et al. cohort with the shop workers excluded, the unit risk predicted for diesel exhaust exposure goes up 3-fold for the air exposure metric and 8-fold for the lung burden metric, as compared to OEHHA's calculated unit risk for the complete cohort. Not only does this inverse dose-response invalidate the OEHHA analyses based on the Garshick epidemiology, but it also indicates that the relative risks reported by Garshick et al. are likely due to causes unrelated to diesel-exhaust exposure. Because the Garshick et al. (1988) epidemiology data set does not show a dose-response for the diesel exhaust exposures calculated by OEHHA, there is no support for the unit risk derived by OEHHA. (Letter from John A. Knebel, President, dated October 13, 1994, p. 2, and "Summary Criticisms of the CARB/OEHHA Diesel Risk Assessment," prepared by Gradient Corporation, pp. 1, 3, and "Critique of the California Environmental Protection Agency 'Health Risk Assessment for Diesel Exhaust,' June 1994," prepared by Gradient Corporation, p. 2)

Response: As pointed out in the TSD, a substantial proportion of the shopworkers were not exposed to diesel exhaust. The revised TSD shows that, due to their very heterogeneous exposure, the overall risk of shopworkers is most likely to be about the same as for train workers. On this basis, the very small reduction of risk with shop workers removed, as reported in Garshick et al. (1988), is well within the random variation of the data.

OEHHA staff were unable to replicate the three-fold and eight-fold increases in estimated unit risk suggested by the comment.

2. Comment summary: Review of epidemiological data on carbon black workers indicates that extrapolation of human risk from animal data is not appropriate. OEHHA bases its unit risk on diesel exhaust particulate concentrations. The absence of lung cancers in occupationally exposed carbon black workers weakens the link suggested by rat data between lung tumors and inhaled particulate. The same animal model that showed inhaled diesel particulate at high concentrations to be carcinogenic in rats has also shown that rats inhaling carbon black particles (with only trace amounts of adsorbed organics) also develop lung tumors at equivalent ambient air concentrations. Data showing that carbon black and diesel exhaust are of equivalent carcinogenicity in rats would predict similar cancer potency factors for carbon black and diesel exhaust. The validity of the rat-human extrapolation for diesel exhaust can be tested by examining whether a similar rat-human extrapolation for carbon black is concordant with lung cancers in workers exposed to carbon black. Workers occupationally exposed to carbon black, either in its manufacture or use, have been evaluated in several epidemiological studies. The findings from these studies indicate that the risk of lung cancer was not elevated in workers exposed to carbon black particles. The same is

true for coal workers. It should be noted that under conditions of obvious lung retention of coal dust in coal miners, an excess in lung cancers has not been detected. This suggests that, unlike the situation with rats, particle mass overload in human lungs does not necessarily lead to lung tumors.

Another approach to examining the validity of the rat-to-human extrapolation is to apply the predictions of OEHHA on diesel-exhaust carcinogenicity to the workers in the carbon black industry, and determine to what degree the predictions for lung cancers are borne out. The commenter's analysis in this regard used data from a 1980 study of carbon black workers. Assuming that carbon black particulate carries the unit risk assigned to diesel exhaust by OEHHA, the lung-cancer rates that would be predicted for carbon black workers (excess risk of 7.14×10^{-2} per person) are much higher than industry experience (114 cases would be predicted; in the study population, 13 were observed). A likelihood analysis showed that it is virtually certain that the rat data on tumorigenicity of carbon black do not correctly predict lung cancers in carbon black workers. Thus, the validity of using the rat model of particle-induced carcinogenesis for human risk assessment is highly questionable.

If one postulates that the insoluble carbon core is responsible for the lung tumors observed in rats, one has to acknowledge the evidence of species differences in response to particle exposure. Before regulatory actions are considered, the apparent absence of an increased risk of lung cancer in human populations occupationally exposed to insoluble particles, such as coal dust or carbon black, should be better understood. (Letter, p. 2, Summary Criticisms, p. 2, and Critique, pp. 2, 7-12)

Response: In response to this and related comments, Chapter 7 of Part B now discusses the question of rat-to-human extrapolation that is raised by the apparent differences in the comparative carcinogenicity of the two different substances in the two species. Also in response, the new Appendix C of Part B summarizes the limited literature on occupational cancer epidemiology of carbon black exposure, adding a new study which found some increase in risk for all lung cancers and a significantly greater risk for one histological type of lung cancer in carbon black workers with a relatively high exposure. Appendix C also provides alternative calculations for comparing the lung cancer deaths observed in the carbon black workers of Robertson and Ingalls (1980) to predictions based on risk estimates from the Garshick et al. (1987) cohort study. These calculations show that for many reasonable assumptions the predictions for diesel exhaust do not differ substantially from the observed lung cancer deaths among the carbon black workers and for other reasonable assumptions the predictions do differ substantially from the observations. Although the comment's point about an apparent difference in human response to diesel exhaust and carbon black is a valuable one, we note here three objections to the commenter's calculation using the upper confidence limit for unit risk for diesel exhaust in the TSD and conclusion that the observed deaths in the carbon black workers differed very substantially from the predictions of the TSD based on the Garshick et al. (1987) cohort study: (1) The calculation of the effective exposure for the. carbon black workers did not take into account the progressively increasing cumulative exposure for all workers but rather used the ending cumulative exposure for all years of followup. (2) The calculation used a very high level of exposure for a long time and did not survey any range of alternatives. (3) The calculation used the 95% UCL of unit risk for diesel exhaust; the MLE would have been appropriate. The comparison in Appendix C uses a new and somewhat lower value for diesel exhaust unit risk with more appropriate measures of exposure, and finds much smaller differences (not all of which are substantial) than the difference found by the commenter.
Nevertheless, the new results do suggest there could be a difference in human response.

The possibility cannot be excluded that genotoxicity due to the PAH and nitroPAH content of diesel exhaust plays a role in the induction of lung tumors in rats at lower levels of diesel exhaust. This mechanism would probably be relevant to human cancer risk, and would not be expected to have a threshold of action. Chapter 3 of Part B discusses bioavailability and metabolic activation of particle-associated organics, and Chapter 5 describes extraction under physiological conditions of mutagens from diesel exhaust. Chapter 5 also cites findings of increased lymphocyte DNA adducts in humans occupationally exposed to diesel exhaust. This is a fundamental difference between diesel exhaust and carbon black exposures, and indicates that comparing rat and human responses to carbon black exposure may not be completely applicable to determining if rat lung tumor response to diesel exhaust exposure accurately models human cancer risk. Thus it is not clear that the validity of rat-to-human extrapolation for diesel exhaust can be tested by examining whether a similar rat-to-human extrapolation for carbon black is concordant with lung cancers in workers exposed to carbon black.

The situation regarding the assertion of lack of elevation of lung cancer rates in coal worker studies is different. Coal dust has very different characteristics, especially in particle size and shape (for example, specific surface), compared to either diesel exhaust or carbon black. So it should not be expected to have the equivalent toxicity. The generally large particle size suggests a more central deposition pattern in the lung. The different shape may suggest different carcinogenic potential, especially if surface area is important. Thus a finding of no detectable carcinogenic effect in coal miners appears unlikely to bear on the issue of carcinogenicity of diesel exhaust.

3. Comment summary: Inclusion of squamous cysts in the group of animal lung tumors leads to overstated unit risk. OEHHA's unit risk predictions based on animal data are flawed because the lung lesions developed by the rats are not analogous to human cancers. The carcinogenicity of diesel exhaust in rats is based on counting all tumors observed, both benign and malignant. Lung pathologists in the U.S. generally agree that squamous cysts in rat lungs are a nonneoplastic lesion that should not be included in the lung tumor category. A cancer potency factor calculated without squamous cysts would be about 1.3 times lower than with squamous cysts. Although the effect of excluding squamous cysts is not large, inaccurate data should not be included in risk calculation. Diesel exhaust risk estimates that include squamous cysts in the number of total tumors are biased high. In addition, the anatomical location and distribution of tumor types that were seen in the rat lungs are not typical of the lung cancers seen in humans. In rat studies, lung tumors occurred in the periphery of the lung. Although the incidence of bronchoalveolar carcinomas may be rising in humans, they represent only 2-5% of primary lung cancers; most human lung neoplasms occur in the central airways. We do not know if this difference in tumor location is based on differences in dose distributions, which are governed by anatomical differences, or species differences in lung cell susceptibility to carcinogenic events. The applicability of the rat data to human populations should be more fully substantiated before the potential carcinogenicity of diesel exhaust can be quantitatively predicted. (Letter, p. 2, Summary Criticisms, pp. 2-3, and Critique, pp. 2, 7-8, 15)

Response: A definitive consensus on whether squamous cysts are precursors to squamous cell carcinoma has not been reached. However, the presence of the cysts is clearly treatment-related,

and the possibility exists that higher doses of diesel exhaust reduce the latency period for transformation of squamous cysts to squamous cell carcinomas. This may possibly suggest that the squamous cysts could be precancerous lesions. There is controversy among scientists on this point. For comparison purposes, thus, the TSD (Part B, Chapter 7) notes that potency estimates derived from rat lung tumor data including squamous cyst incidence are approximately 30% higher than potency estimates that do not include the cysts. However, the range of values reported in the TSD includes only unit risk estimates that are based on excluding the cysts.

4. Comment summary: This commenter has major concerns about Part B's treatment of species extrapolation. The rat may be unique in its lung tumor response to diesel exhaust exposure. Certain data from hamsters and mice support this or are equivocal. Several lines of evidence suggest that differences in biological responses occur and may be critical when extrapolating from rat models of particle-induced lung tumors to human exposures. Thus, the validity of extrapolating from the rat model to humans must be seriously questioned. There are clear differences among animal species both in their tumor response to inhaled particles and the degree of lung inflammation and lung fibrosis in response to inhaled diesel exhaust. Only rats get lung tumors when exposed to diesel exhaust, and this response is not unique to diesel particles but can be demonstrated when rats are chronically exposed to other insoluble particles. Excessive lung burdens of particles is a uniform finding in particle-induced lung cancer in rats. It may not be particle-induced lung overload *per se,* but a species-specific reaction of the prolonged presence of particles that is critical to the tumors induction in rats. Recent theories on nongenetic mechanisms of carcinogenesis emphasize the importance of inflammatory and proliferative responses of target tissues. In long-term inhalation studies, diesel-exposed hamsters did not develop lung tumors, but they exhibited a delayed clearance of tracer particles, suggesting lung overload. Hamsters also exhibited a more modest inflammatory response and less epithelial cell proliferation than rats. Recently, when rats and mice were chronically exposed to diesel exhaust, titanium dioxide, or carbon black particles, at identical particle concentrations resulting in similar particle loads per gram of lung tissue, the mice did not show an increased lung tumor response. Therefore, tissue responses to lung particles, which may be species specific, are probably a key ingredient in tumor susceptibility. Additional support for species specificity in response to lung particles has been demonstrated. Rats and mice were exposed to identical concentrations of diesel exhaust, which resulted in similar lung burdens. However, various measures of oxidative stress showed that diesel exposed mice had a greater capacity to accommodate an oxidative insult than diesel exposed rats; the lungs from the mice also showed a minimal fibrotic response in comparison to rats. Because tumor induction by inhaled diesel exhaust particles is limited to rats, it is uncertain whether such a response is generalizable to humans. Furthermore, there are apparent differences between rats and humans in the carcinogenic response to exposure to inhaled particles. (Letter, p. 2, Summary Criticisms, p. 3, and Critique, pp. 1-2, 4, 6-7).

Response: As stated in response to Comment 2, the possibility cannot be excluded that genotoxicity due to the PAH and nitroPAH content of diesel exhaust plays a role in the induction

of lung tumors in rats at lower levels of diesel exhaust. Note that mechanisms of carcinogenesis and sensitivity to carcinogens may differ among species, as indicated by the commenter. However, in addition to the data in rats, human epidemiological data also point to diesel exhaust as likely to be a carcinogen.

There is evidence that the biological effects of diesel exhaust are not due solely to a particle effect, particularly with regard to measures of inflammation and allergic responses in the upper airways. These effects are discussed in Chapter 4. Additionally, intratracheal instillation of diesel exhaust particulate matter in mice has been shown to inhibit lung antioxidant enzymatic activity (Sagai et al., 1993). In the same study, pretreatment with superoxide dismutase (SOD), an antioxidant enzyme, or butylated hydroxytoluene (BHT), a radical scavenger, significantly reduced mortality in diesel exhaust particulate matter-treated mice. Exposure of mice to diesel exhaust particles by intratracheal instillation resulted in a significant increase (approximately 3-fold) in mouse lung DNA 8-OHdG adducts (Nagashima et al., 1995). Although, as the commenter suggests, interspecies differences in inflammation and response to oxidative stress may be important, insufficient data are available to account for these differences, in animal-to-human risk assessment.

5. Comment summary: The published evidence rejects the genotoxic character of diesel-particle action, supports the existence of epigenetic tumorigenesis from exposure in animals, and reaffirms the presence of a no-effect level at low ambient diesel exposures. (Letter, p. 2)

Response: The TSD has been revised to include discussion of 1) studies which indicate that extraction with a phospholipid emulsion resembling a major component of lung surfactant showed substantial mutagenic activity, sometimes greater than that observed after extraction with organic solvents (Chapter 5); 2) data indicating that both animal and human occupational exposure to diesel exhaust has been shown to result in the production of urinary metabolites of PAHs and nitroPAHs, indicating bioavailability of those compounds (Chapter 3);
3) studies which show that formation of human lymphocyte DNA adducts is associated with occupational exposure to diesel exhaust (Chapter 5). This information suggests that the induction of lung cancer in humans associated with diesel exhaust exposure may occur through a non-threshold genotoxic mechanism. This genotoxicity may also contribute to at least part of the rat lung cancer response to diesel exhaust exposure, and it should be noted that genotoxic effects are generally not considered to have a no-effect level. In addition, the proposed overload mechanism includes chronic inflammation and associated production of inflammatory cytokines and increased cell proliferation. As noted in a recent paper by Gaylor and Zheng (1996), (1) a threshold dose is questionable if a carcinogen acts via a cell receptor, (2) even a nongenotoxic carcinogen that increases the cell proliferation rate by augmenting an endogenous mechanism is not likely to have a threshold dose, and (3) dose response curves for cell proliferation and tumor incidence do not necessarily mimic each other.

6. Comment summary: The effort to produce Part B of the TSD was thorough, and the authors were careful to note their rationale for certain choices and to solicit public comment on areas of uncertainty. The detailed mathematical modeling in the document gives the illusion of precision. Closer examination shows that the usefulness of the quantitative results is limited by serious

shortcomings in the animal and human toxicology data bases. The biological uncertainties are so significant that it would be premature to list diesel exhaust as a toxic air contaminant. (Letter, p. 2, Summary Criticisms, p. 3, and Critique, pp. 1-2).

Response: There are uncertainties involved in the risk assessment for diesel exhaust, as with any quantitative risk assessment. The data showing carcinogenic effects of diesel come from both animal and human studies. The non-cancer effects are varied, observed in several species and clearly evident from the animal studies and human case reports.

The revised report documents the animal and human evidence that supports a finding that diesel exhaust may cause or contribute to an increase in mortality or in serious illness, or may pose a present or potential hazard to human health. Thus we believe that diesel exhaust meets the definition of a toxic air contaminant.

7. Comment summary: The commenter wishes to go on record in support of the comments submitted on the proposal by a large coalition of industry organizations, of which this commenter is a member. The commenter also wishes to go on record in support of, and incorporates by reference as part of its own comments, the individual comments filed by The Association of American Railroads, The Engine Manufacturers Association, The Western States Petroleum Association, The California Trucking Association, and Mercedes Benz. To the extent the commenter's positions differ from those of the referenced organizations, the commenter stands by its own testimony and documentary evidence. (Letter, p. 2).

Response: Please see responses to the referenced comments.

8.. Comment summary: The organics extracted from diesel particles by harsh solvents do not accurately reflect the bioavailability of particle-associated compounds in lung fluids. For regulations (if they are to be imposed), we need to understand how bioavailability of organic compounds, under physiologic environments, varies with different diesel engine emission products. (Critique, p. 1).

Response: As noted in response to Comment 5, the TSD has been revised to include discussion of 1) studies which indicate that extraction with a phospholipid emulsion resembling a major component of lung surfactant showed substantial mutagenic activity, sometimes greater than that observed after extraction with organic solvents (Chapter 5); 2) data indicating that both animal and human occupational exposure to diesel exhaust has been shown to result in the production of urinary metabolites of PAHs and nitroPAHs, indicating bioavailability of those compounds (Chapter 3); 3) studies which show that formation of human lymphocyte DNA adducts is associated with occupational exposure to diesel exhaust (Chapter 5).

It is likely that the composition of diesel exhaust varies somewhat with engine (source) type, year and fuel formulation. Whether these variations importantly impact the bioavailability of diesel particle-associated organic compounds or the risks associated with diesel exhaust cannot be assessed without appropriate tests of the exhausts at issue and an index of the toxicological concern associated with each of the measured components. Because this information is not

available, we have not been able to take into account, in the risk assessment, differences among different types of diesel engines, model years, or fuels. The Air Resources Board is sponsoring work to speciate the components of current diesel exhaust.

Part B of the TSD discusses genotoxicity studies which indicate that changes in diesel fuel composition have not been demonstrated to eliminate exhaust genotoxicity, and that changes in engine type and year have a relatively small effect on the magnitude of diesel exhaust genotoxicity (see Chapter 5). The TSD also discusses studies on rats which largely found similar doses of diesel exhaust to have about the same carcinogenic effects even though several different engine types and fuels were used to generate diesel exhaust (see Chapter 6).

Part B does address the composition of diesel exhaust, including the several fractions of diesel exhaust. Studies describing increased lung tumor incidence in mice and increased incidence of splenic malignant lymphomas in rats when exposed to filtered diesel exhaust are discussed in Chapter 6. Studies indicating that the semivolatile phase of diesel exhaust is genotoxic are discussed in Chapter 5. It should be noted that there are PAH and nitroPAH components of the several phases of diesel exhaust which have not been evaluated individually for carcinogenicity. Also, it is probable that the chemical speciations of diesel exhaust performed to date have not reported every PAH, nitroPAH and related compounds present in diesel exhaust.

9. Comment summary: If lung tumor formation is dependent on the occurrence of lung overload, then there are exposure concentrations below which the lungs can effectively clear deposited particles and not be susceptible to lung tumors. The animal dose-response data are supportive of a threshold. (Critique, p.1)

Response: The premise of the comment, that lung tumor formation is completely dependent on the occurrence of lung overload, is questionable. While some of the animal data may be supportive of a threshold model, other data suggest otherwise. For example, the possibility cannot be excluded that genotoxicity due to the FAH and nitroPAH content of diesel exhaust plays a role in the induction of lung tumors in rats at lower levels of diesel exhaust. This mechanism would probably be relevant to human cancer risk, and would not be expected to have a threshold of action. Chapter 3 of Part B discusses bioavailability and metabolic activation of particle-associated organics, and Chapter 5 describes extraction under physiological conditions of mutagens from diesel exhaust. Chapter 5 also cites findings of increased lymphocyte DNA adducts in humans occupationally exposed to diesel exhaust.

10. Comment summary: This commenter has major concerns about Part B's treatment of mechanisms of action. The document vacillates between the tumorigenic potential of genotoxic compounds and the tumorigenic potential of a lung burden of insoluble particles. It uses both types of evidence to support the view that diesel exhaust represents a health hazard. However, it does not apply the evidence in a consistent fashion. For example, if risk assessments and regulations are to be based on the particulate fraction of diesel exhaust, then what is the purpose of detailing the potential genotoxicity of the associated organic fraction? The fact remains, we do not know which is relevant for human exposures.

Caution must be used when using DNA adducts as a surrogate for tumorigenic potential. The absence of a dose-response and of a correlation between adduct levels and tumor formation may have a technological basis (for example, inadequate numbers of animals in bioassays), as suggested in the document, but also may have a biological basis. For example, oxygen free radicals derived from inflammatory cells could form adducts and thus, the response would be unrelated to the dose of particle-associated organic compounds. In addition, events occurring after adduct formation (such as DNA repair) can alter the correlation between DNA damage and tumors. Alternatively, tumor induction may result from a nonspecific response of the lung to the presence of insoluble particles. The vacillation between genotoxic and nongenotoxic mechanisms has important implications for how the document used the results from various studies to support its arguments. (Critique, pp. 1, 3-4)

Response: Although it would be preferable to establish the precise mechanism of carcinogenesis, doing so is not a prerequisite for the selection of a model or estimation of a unit risk value. Both direct genotoxicity (including that associated with both the particulate and semivolatile phases) and particle effect-mediated genotoxicity (including the free radical mechanism suggested in the comment) may be relevant to human responses to diesel exhaust exposure. The descriptions of DNA adduct data in Part B (Chapter 5) are used to describe genotoxicity and to illuminate potential mechanisms of tumorigenicity; DNA adduct data is not used as a surrogate for tumorigenic potential. The TSD is intended to give an assessment of risks at current levels of exposure, and the risk assessment uses the mass of diesel exhaust particles as the measure of exposure. OEHHA staff believe this dose metric is relevant to human toxicity.

11. Comment summary: Within the context of different mechanisms, OEHHA failed to adequately address critical issues. For example, if particle-associated genotoxic compounds are important for tumor induction, then the extent of organics bioavailability in physiological fluids must be understood. Even though certain studies are raised in the document as evidence of genotoxicity, their biological relevance is not discussed. Data derived from solvent-extracted particles is likely irrelevant to our understanding of the biologic toxicity of particle-associated organic compounds in the lung. Furthermore, we need to understand how bioavailability, under physiologic environments, varies with different emission products and different concentrations. When there is a low concentration of particle-associated organic compounds, these molecules are more tightly bound to the surface of the carbon core and thus, are less bioavailable than if there were a high concentration. Therefore, one would expect the particles derived from older "dirtier" engines may have more genotoxic potential than the "cleaner" particles derived from current engines.

If the presence of retained particles is the primary tumor-inducing cause, then the issue of threshold must be resolved. It is unclear what "evidence" of genotoxicity is referred to in the document in conjunction with a statement that "there is likely to be no threshold." If lung tumors in rats are the results of lung overload, the evidence (including certain specific studies) supports the existence of a threshold. Certain data support a specific threshold. It is possible that at low exposures, increases in tumor incidence are at the lower limit of detection; it impractical to design an experiment that would use enough animals to determine whether a positive tumor response occurs at low doses. However, if the formation of lung tumors is dependent on the

occurrence of lung overload, then one can say with reasonable confidence that there are exposure concentrations below which lung clearance is not compromised. It has been predicted that humans, because of their slower clearance of insoluble particles, would achieve greater lung burdens than rats at similar airborne concentrations; however, impaired alveolar clearance resulting from lung overload has not been measured in humans. Impaired clearance functions can only be inferred from observations made in coal miners exposed to high levels of coal dust. Furthermore, human lung-tissue reactions to particle overloading have not been characterized. (Critique, pp. 4-7)

Response: Part B of the TSD has been revised to include discussion of studies which indicate that extraction with a phospholipid emulsion resembling a major component of lung surfactant showed substantial mutagenic activity, sometimes greater than that observed after extraction with organic solvents (Chapter 5). As stated in Part B's Chapter 6, the mechanism of action by which diesel exhaust induces lung tumors in rats is not established. One proposed mechanism is that exposure to diesel exhaust particulate matter at high concentrations exceeds pulmonary clearance capabilities and causes chronic inflammation. This inflammation leads to macrophage and/or neutrophil-induced oxidative DNA damage resulting in mutations which are instrumental in the induction of lung tumors, and also to cell proliferation which may be mechanistically important to the promotion of the rat lung tumors. This mechanism may have an exposure threshold of action, suggesting that tumor induction due to this mechanism would also have a threshold. Although no mechanism has been established to account for the increased rates of lung tumors in diesel exhaust exposed workers, it has been proposed that any modeling of human cancer risk using rat lung tumor data should include a exposure threshold below which tumor induction would not occur. However, the possibility cannot be excluded that genotoxicity due to the PAH and nitroPAH content of diesel exhaust plays a role in the induction of lung tumors in rats at lower levels of diesel exhaust. This mechanism would probably be relevant to human cancer risk, and would not be expected to have a threshold of action; Chapter 3 discusses bioavailability and metabolic activation of particle-associated organics, and Chapter 5 describes extraction under physiological conditions of mutagens from diesel exhaust. Chapter 5 discusses a nuclease Pl-sensitive lung DNA adduct isolated from rats exposed to diesel exhaust; rats exposed to carbon black or $Ti0_2$ did not show the same adduct. Chapter 5 also describes studies demonstrating increased lymphocyte DNA adducts in humans occupationally exposed to diesel exhaust. The rat lung tumor data have not been shown to be mechanistically irrelevant to human cancer risk from diesel exhaust inhalation and with these uncertainties acknowledged, provides information useful in the characterization of the potential magnitude of human cancer risk associated with diesel exhaust exposure.

Regarding the issue of threshold, the cited statement in Part B's introductory chapter has been revised to read, "The in vitro and in vivo genotoxicity of diesel exhaust suggests that a non-threshold mechanism for carcinogenesis may be involved. The Moolgavkar quantitative analyses of the rat cancer bioassay did not suggest there was a threshold for the carcinogenicity of diesel exhaust in the rat." The genotoxicity evidence is discussed in Chapter 5 of Part B. The quantitative analyses are presented in Chapter 7.

As noted in response to Comment 5, information suggests that the induction of lung cancer in humans associated with diesel exhaust exposure may occur through a non-threshold genotoxic mechanism. This genotoxicity may also contribute to at least part of the rat lung cancer response to diesel exhaust exposure, and it should be noted that genotoxic effects are generally not considered to have a no-effect level. In addition, the proposed overload mechanism includes chronic inflammation and associated production of inflammatory cytokines and increased cell proliferation. As noted in a recent paper by Gaylor and Zheng (1996), (1) a threshold dose is questionable if a carcinogen acts via a cell receptor, (2) even a nongenotoxic carcinogen that increases the cell proliferation rate by augmenting an endogenous mechanism is not likely to have a threshold dose, and (3) dose response curves for cell proliferation and tumor incidence do not necessarily mimic each other.

The comment is correct in noting that the TSD does not characterize human lung tissue reactions to particle overloading. The type of overload situation observed at high doses in rats is not thought to occur at the levels to which humans are exposed.

The TSD does not posit any particular mechanism as responsible for diesel exhaust carcinogenesis. The presence of retained particles has not been established as the primary tumor-inducing cause in humans. Epidemiologic studies cited in the document and the new meta-analysis of those studies suggest that humans have experienced levels of diesel exhaust exposure that are associated with lung cancer; any hypothesized threshold above those levels seems implausible. Human exposures in these epidemiologic studies were below levels that would be associated with overload in the human lung. Even if the lung tumors in rats were results of lung overload, the hypothesized overload-bounded threshold in rats would not necessarily be applicable to humans. As the comment suggests, it might indeed be impractical to test enough animals to determine whether a positive tumor response occurs at certain low doses.

12. Comment summary: The cancer models used by OEHHA assumed linear extrapolation from high to low doses for both of two exposure metrics: diesel particle atmospheric concentration and diesel particle lung burden. Given that the chronic rat studies show an apparent threshold, the logic for choosing linear extrapolation is not clear. In fact, OEHHA calculated diesel exhaust lung burden using a model that uses a non-linear relationship between atmospheric concentration and lung burden. By electing diesel particle lung burden as a dose metric, OEHHA acknowledged the role of lung overload, which exhibits threshold characteristics. Thus, the emphasis on linearized models is a self-contradiction. (Critique, p. 15)

Response: Since the chronic rat studies do not allow for direct examination of effects at low doses due to limitations in the power of the studies to detect low-incidence effects, it is not possible to ascertain the existence of a threshold from the data. Linear models are used for extrapolation in absence of information that non-linear models are more appropriate. The models selected by OEHHA, in an effort to estimate the effects at low concentrations, included the Moolgavkar model, which does allow for a threshold term, if a threshold is apparent. In this case, a threshold term was not apparent.

The lung burden calculation from the Mauderly et al. (1957) study is taken from empirical measurements of actual lung burden from that study by the investigator. Lung burden is simply an empirical measurement of particle retention, and does not necessarily imply the presence of an overload phenomenon. Using this metric may help linearize the dose-response curve by adjusting for the non-linearity of lung burden.

13. Comment summary: Although OEHHA stressed the uncertainties associated with scaling from rats to humans, Part B did not adequately address the probable existence of species differences in biosusceptibility. OEHHA chose to use body weight to the 2/3 power to obtain dose-equivalency between rats and humans; yet this contradicts certain recent reviews which have examined this scaling factor, and which conclude that the power should be unity, that is, straight mg/kg-d provides the best expression of dose equivalency. Scaling adjustments were discussed, but species differences in the response to lung overload were not discussed. The absence of lung cancers in occupationally exposed carbon black workers weakens the link suggested by rat data between lung tumors and inhaled particles. Epidemiological data for carbon black workers indicate that extrapolation of human risk for inhaled particles from rat bioassay data is not appropriate. (Critique, pp. 15-16)

Response: The reviews (by Goodman and Wilson) cited in the comment do not conclude that the scaling factor should be unity. The authors (in Environ. Health Perspect. 94:195-218, 1991) assert, from a cursory survey of the animal and human cancer literature, that a central estimate for interspecies scaling could be unity rather than a factor based on surface area. The authors also conclude that if unity were used as a default, a 20-fold range of uncertainty should be placed about this estimate for conservative public health decisions. The authors state that "...the best estimate for an interspecies uncertainty factor is an unknown, to be determined from existing data." In absence of such data, use of the surface area scaling factor (the 2/3 power) does not contradict the reviews. It is within the authors' range.

The comment is correct in noting that species differences in the response to lung overload were not discussed in the TSD. The type of overload situation observed at high doses in rats is not thought to occur at the levels to which humans are exposed.

Chapter 7 of Part B now discusses the question of rat-to-human extrapolation that is raised by the apparent differences in the comparative carcinogenicity of diesel exhaust and carbon black in the two species. Also, the new Appendix C of Part B summarizes the limited literature on occupational cancer epidemiology of carbon black exposure, adding a new study which found some increase in risk for all lung cancers and a significantly greater risk for one histological type of lung cancer in carbon black workers with a relatively high exposure. Appendix C also provides alternative calculations for comparing the lung cancer deaths observed in the carbon black workers of Robertson and Ingalls (1980) to predictions based on risk estimates from the Garshick et al. (1987) cohort study. These calculations show that for many reasonable assumptions the predictions for diesel exhaust do not differ substantially from the observed lung cancer deaths among the carbon-black workers and for other reasonable assumptions the predictions do differ substantially from the observations.

14. Comment summary: OEHHA's risk estimate derived from the Garshick et al. (1988) study is based on exposure to emissions from locomotive engines between 1945 and 1980. Although OEHHA reconstructed concentration levels of diesel particulate to which the railroad workers were exposed during the study period, no information exists concerning either the actual exposure levels or the nature of the diesel particulate. The general public and most occupational exposures are to diesel emissions derived from heavy-duty engines, which have not been used for either an animal-based or epidemiology-based risk assessment. Furthermore, the impact of reformulated diesel fuel and changes in engine design on human exposure levels and potential toxicity are unknown. It seems inappropriate to base a human risk estimate on the emissions of a no longer used, outdated technology. (Critique, p. 16)

Response: It is likely that the composition of diesel exhaust does vary somewhat with engine (source) type, year and fuel formulation. Whether these variations importantly impact the risks associated with diesel exhaust cannot be assessed without quantitative speciation of the components of the exhaust at issue and an index of the toxicological concern associated with each of the measured components. Because this information is not available, we have not been able to take into account, in the risk assessment, differences among types of diesel engines, model years, or fuels. The Air Resources Board is sponsoring work to speciate the components of current diesel exhaust.

Changes in engine design could reduce or heighten the risk associated with a given mass of diesel exhaust particles (e.g., by producing particles of different size).

15. Comment summary: Part 8 did not discuss recent efforts by the U.S. EPA to derive a unit risk estimate using data from the Garshick et al. studies. The U.S. EPA was unable to obtain an adequate dose-response curve and concluded that the epidemiologic data are "inadequate for quantitative risk assessment." The OEHHA document does not address or clarify differences in opinion between the federal and state agencies on the feasibility of conducting risk assessments from human studies. (Critique, p. 16)

Response: The 1994 TSD did not specifically address differences with U. S. EPA concerning use of the human data because its draft Health Assessment Document for Diesel Exhaust was not available when the TSD went to press. As pointed out in a discussion in the new version of the TSD, an OEHHA investigation found an error in one part of the Crump et al. (1991) report that made that part, with statistically significant negative slopes, invalid. Nevertheless, the use of the Garshick et al. (1988) cohort data for quantitative risk assessment remains a controversial issue.

16. Comment summary: Regarding OEHHA's derivation of a cancer slope factor from the results reported by Garshick et al. (1988), the data fail to support a positive relationship between diesel exposure as calculated by OEHHA and the relative risk of lung cancer. Although the relative risk of lung cancer increases as a function of OEHHA's measure of diesel exposure for the entire population of exposed workers described in the Garshick et al. study, analysis of this relationship among only moderately exposed workers reveals important inconsistencies. Surprisingly, when compared to "unexposed workers" (clerks, ticket agents, dispatchers, station agents, and station telegraphers), the relative risk of lung cancer for moderately exposed workers only (engineers,

firemen, brakemen, and conductors, excluding the highly-exposed shopworkers and hostlers) is at least as great as the relative risk of lung cancer for the .entire population of exposed railroad workers. That is, the relative risk of lung cancer does not increase as a function of the exposure level as calculated by OEHHA. (Critique, p. 17)

Response: As pointed out in the TSD, a substantial proportion of the shopworkers was not exposed to diesel exhaust. The revised TSD shows that, due to their very heterogeneous exposure, the overall risk of shopworkers is most likely to be about the same as for train workers.

17. Comment summary: It should be noted that Woskie et al., the researchers whose data formed the basis for OEHHA's exposure estimates for the Garshick et al. cohort, considered using historic information to adjust their exposure estimates for temporal variations, as did OEHHA, but did not because they judged the data to be too limited and to contain too many potential errors to be used for quantitative analysis. (Critique, p. 20)

Response: Woskie et al. wrote of the limitations of industrial hygiene data. This is one of the reasons OEHHA staff chose to use dieselization data instead. One of Woskie's co-authors, Thomas J. Smith, presented dieselization data in January 1996 at the technical workshop in San Francisco, "Diesel Exhaust: Considerations in the Use of Epidemiologic Data for Quantitative Risk Assessments," that was co-sponsored by OEHHA.

18. Comment summary: For the purpose of calculating average exposure for the entire Garshick et al. cohort, OEHHA assumed that one half of all shop workers were unexposed. No justification is given for this assumption, nor is it supported by the job descriptions or exposure concentrations reported by Woskie et al. (Critique, p. 21)

Response: The TSD now gives the rationale for this. See Part B, Chapter 7.

19. Comment summary: The commenter evaluated the robustness of the dose-response relationship inferred by OEHHA from the Garshick et al. data by characterizing the relationship for all exposed workers *excluding* shop workers. (Garshick et al. reported relative risk values for all exposed workers, excluding hostlers as well. It is unlikely that adding the hostlers back in would substantially alter the relative risk values since there were only 780 hostlers in the entire cohort, a relatively small number compared to the 29,290 exposed workers who did not work in the repair shops. Because the hostlers were exposed to very high levels of particulate, adding them back into Garshick's analysis should, if anything, increase the relative risk values for the subgroup of workers.) The dose-response relationship implied by the relative risk values found by the commenter is not consistent with the dose response relationship inferred by OEHHA from the values corresponding to the entire exposed worker cohort. In terms of both atmospheric concentration and (most dramatically) lung burden, excluding the shop workers substantially decreases average cohort exposure, but has little impact on relative risk.

There are several possible explanations for the inconsistency. First, it is possible that the historical atmospheric diesel concentrations inferred by OEHHA are inaccurate. Second, it is possible that although risk of lung cancer does increase as a function of exposure to diesel,

OEHHA has not identified an appropriate measure of exposure. Finally, it is possible that, at least in the range of exposure experienced by the Garshick et al. cohort, diesel exhaust exposure does not increase the risk of lung cancer. The fact that the dose-response relationship appears to be completely flat (as opposed to upward-sloping but statistically insignificant) makes this third explanation highly plausible. Moreover, the absence of an upward-sloping dose-response relationship is most clearly illustrated when we measure exposure in terms of lung burden, OEHHA's favored index. The changes in relative risk over time reported by Garshick et al. may be related to other factors aside from diesel exhaust exposure, such as changes in time due to cigarette smoking in the exposed or in the comparison cohort.

It also is helpful to look at the inconsistencies of OEHHA's derivation from a risk assessment point of view. Of the exposed subgroups of railroad workers, the shop workers and hostlers were groups with greatest exposure, and the OEHHA analysis shows that when compared to other diesel-exposed workers, their predicted lifetime exposures were 15 times larger, based on cumulative air exposure and 22 times larger, based on lifetime lung burden. However, Garshick et al. reported that, with the shop workers excluded, the relative risk actually went up a little rather than down. Therefore, if the OEHHA analysis is applied to the Garshick et al. cohort with the shop workers excluded, the unit risk predicted for diesel exhaust exposure goes up 3-fold for the air exposure metric and 8-fold for the lung burden metric. This makes no sense. The Garshick et al. data, as analyzed by OEHHA, directly contradict OEHHA's own estimate of diesel exhaust health risks. This contradiction invalidates OEHHA estimates, and indicates that the relative risks reported by Garshick et al. are likely due to effects not related to diesel exhaust exposure. (Critique, pp. 16-26)

Response: As pointed out in the TSD, a substantial proportion of the shopworkers were not exposed to diesel exhaust. That portion of shopworkers who were very highly exposed undoubtedly did experience a disproportionately high lung burden. However, quantifying that excess is highly problematic, and the new version of the TSD (Section 7.3) does not attempt to estimate lung burden in humans. OEHHA staff were unable to replicate the three-fold and eight-fold increases in estimated unit risk suggested by the comment. There is not enough information on the shop workers to support a contradiction of the analysis of other data from the Garshick et al. (1988) cohort. One primary calculation of unit risk in Section 7.3 uses the case-control study report by Garshick et al. (1987a), which includes shopworkers, because that is one of the few available published human study reports from which to calculate unit risks for diesel exhaust. New analyses in Appendix E and in Section 7.3 do not include shopworkers in principal results because of the highly variable exposure in that group.

20. Comment summary: Although Part B of the draft TSD concludes that "there is insufficient basis for determining that the carcinogenic effect has a threshold" because of "evidence of genotoxicity and of quantitative analysis of the cancer bioassay," experimental evidence unequivocally shows and the scientific community recognizes that a threshold exists below which diesel exhaust exposure produces no carcinogenic response. This suggests that the evidence "of genotoxicity and of quantitative analyses of the cancer bioassay" is based on an incomplete evaluation of available information.

The existence of a measurable threshold in the tumor-producing action of diesel exposures has been adequately demonstrated for the following reasons: (a) Diesel exhaust produces tumors by secondary "overload" mechanisms that occur in high exposures and cannot be extrapolated to low ambient concentrations. (b) Animal experiments document a finite no-effect level at low-level exposures. Even when pooled together, the experiments show no effect at low concentrations. (c) Deposition models indicate a "critical dose" that exceeds the ambient concentrations by orders of magnitude. This critical dose cannot be achieved by ambient exposures.

There is considerable evidence for a no-effect level in animal bioassays There is no risk that the public health will not be adequately protected because projected ambient concentrations are well below the observed tumor response. The existence of a finite threshold in diesel-induced carcinogenesis has been predicted by the identified epigenetic mechanisms, confirmed by dose-response relationships in animal studies, reaffirmed by the identification of the overload mechanisms, and quantitatively verified by new deposition models. These conclusions question the TSD's view that quantitative analyses of animal bioassays do not support a no-effect level in the tumor-producing action of diesel exposures." Prudent science policy suggests that either a real no-effect level (threshold) is recognized for the diesel exhaust-induced animal tumors or the tumors should not be included in dose-response extrapolations for the estimation of human cancer risk. ("The Evidence for a No-effect Level (Threshold) in Diesel Particle Lung Carcinogenicity," prepared by J.J. Vostal, Environmental Health Consultants Int'l, p. 2-3, 11-18)

Response: As noted in the new draft Part B's introductory chapter, the issue of a threshold is a source of uncertainty. The chapter now concludes, "The in vitro and in vivo genotoxicity of diesel exhaust suggests that a non-threshold mechanism for carcinogenesis may be involved. The Moolgavkar quantitative analyses of the rat cancer bioassay did not suggest there was a threshold for the carcinogenicity of diesel exhaust in the rat. ... at present, the limited evidence available does not allow a threshold for carcinogenesis to be identified."

As stated in Chapter 6, the mechanism of action by which diesel exhaust induces lung tumors in rats is not established. As noted in a recent paper by Gaylor and Zheng (1996), (1) a threshold dose is questionable if a carcinogen acts via a cell receptor, (2) even a nongenotoxic carcinogen that increases the cell proliferation rate by augmenting an endogenous mechanism is not likely to have a threshold dose, and (3) dose response curves for cell proliferation and tumor incidence do not necessarily mimic each other. In addition, the possibility cannot be excluded that genotoxicity due to the PAH and nitroPAH content of diesel exhaust plays a role in the induction of lung tumors in rats at lower levels of diesel exhaust. There is evidence that the biological effects of diesel exhaust are not due solely to a particle effect, particularly with regard to measures of inflammation and allergic responses in the upper airways. These effects are discussed in Chapter 4 of Part B. it might be impractical to test enough animals to determine whether a positive tumor response occurs at certain low doses. The power of the rat bioassays conducted to date has been insufficient to detect low levels of increased tumor incidence, so a conclusion from the bioassay data about a lack of effect at low concentrations of diesel exhaust could be uncertain at best.

21. Comment summary: Contrary to the 1985 Department of Health Services guidelines that permit no other characterizing of diesel exhaust than as a chemical carcinogen and reject the existence of a threshold, current science recognizes alternative mechanisms of carcinogenicity. Introduction of these epigenetic mechanisms into the risk assessment process has been postulated by scientific community since 1990, was recently accepted by other governmental agencies such as U.S. EPA, and was proposed for diesel exhaust in 1983 and reaffirmed by experimental data in 1992-94. The scientific community and Federal agencies have already rejected the inappropriate use of linearized multistage models of chemical carcinogenesis for the assessment of the impact of diesel exhaust on public health. The California DHS guidelines should be updated to include other than genotoxic mechanisms. OEHHA staff need more time to reassess new information on the progress in understanding cancer. The OEHHA document should be modified either to identify the existence of a no-effect threshold for low diesel exposures or to characterize animal tumors produced by overload mechanisms in a single animal species as a unique effect that does not contribute to the quantitative weight of evidence that diesel exhaust poses a human carcinogenic hazard.

The TSD should consider an epigenetic mode of action as an alternative mechanism of diesel exhaust carcinogenicity. The uncertainties noted in the document regarding the carcinogenicity of diesel exhaust are primarily related to the fact that positive findings of tumors have been reported only in one animal species, i.e., the laboratory rat. In spite of progress in the understanding of carcinogenicity, California Guidelines for Chemical Carcinogen Risk Assessment continue to agree with the International Agency for Research on Cancer that "there is not, at present, sufficient scientific basis to warrant the separation of carcinogens into two distinct classes ('genetic' and 'epigenetic') for which separate methods of risk assessment are used" and conclude that assessments "will not include the concept of thresholds for carcinogenesis unless clear and convincing evidence is presented to demonstrate their existence for a specific carcinogen in specified circumstances." Experimental data provide more than "clear and convincing evidence" that alternative mechanisms are plausible and should be accepted. Important precedents for policy change (including the U.S. EPA and alpha-2-microglobulin-induced male rat renal tubule tumors) already exist and threshold assuming models have been proposed for documented evidence of hormonal imbalance or cytotoxicity.

Animal data testing the carcinogenicity of diesel exhaust support the plausibility of epigenetic (non-genotoxic) mechanisms. Long-term exposures with high particle loads block lung clearance, lead to an excessive accumulation of particulate matter in the lung and result in formation of lung tumors. However, the tumor action is independent of the presence of chemical carcinogens and occurs whenever inert materials accumulate in the lung. The tumors appear due to physical rather than chemical qualities of the tested material and irrespective of the presence of extractable soot. (Vostal, pp. 2, 3, 4-7, 17, 18)

Response: The comment on the "inappropriate use" of linearized multistage (LMS) models to extrapolate human cancer risk from rat lung tumor data is inaccurate. Note that no Federal regulatory agency has rejected LMS models for diesel exhaust. The World Health Organization is using these models.

The TSD is not addressing whether to revise the 1985 DHS California Guidelines for Chemical Carcinogen Risk Assessment. The data for diesel exhaust do not argue for deviation from standard risk assessment practice as convincingly as do the data for alpha-2-microglobulin.

22. Comment summary: Contrary to the alleged genotoxicity of diesel exhaust based on testing extracts of diesel particles, experimental evidence demonstrates the lack of involvement of the extractable fraction in the carcinogenic process for the following reasons: (a) Only laboratory-prepared extracts of diesel particles contain mutagenic compounds, but these extracts are not easily available in in vivo conditions. Mutagenicity is minimal or absent when tested in extracts obtained with biological fluids and disappears completely 48 hours after diesel particles are phagocytized by alveolar macrophages. Whole diesel particles are not genotoxic in laboratory tests. (b) Adduct formation reported in the literature is not specific for diesel particles or extractable organic fraction and cannot be used as evidence of a primary genotoxicity of diesel exhaust. The specificity of DNA adducts needs to be investigated further. (c) Animal exposures with carbon black and other particles reaffirm that the high lung burden of particles is the principal cause of lung tumors in laboratory rats and that the particle-associated organic compounds do not contribute to an increased tumor formation.

Reevaluation of available information in the light of new understanding of chemical carcinogenicity leads to a conclusion that the published evidence questions the genotoxic character of diesel particle action, supports the existence of epigenetic origin of tumor-producing diesel exposures in animals, and reaffirms the presence of a no-effect level at low ambient diesel exposures. The OEHHA document should reflect this progress in understanding of carcinogenicity and recognize the following: (A) Diesel exhaust 'induces tumors in animal bioassays by epigenetic mechanisms of particle overload with subsequent exaggerated response by alveolar macrophages and not by the genotoxicity of chemicals adsorbed on the particle surface. The role of genotoxic mechanisms of chemicals in the diesel extractable fraction has been excluded by experimental evidence. (B) These tumor-producing "overload" mechanisms are specific solely for laboratory rats, have not been replicated in other animal species and do not exist in humans. Therefore, the animal tumors cannot be used for a correct assessment of human risks. (C) The epigenetic character of tumors, new deposition models, and animal data adequately document a distinct no-effect level for diesel exposures below which no lung cancer occurs. This level cannot be reached by ambient exposures. (Vostal, pp. 2, 3, 11, 18)

Response: There is evidence that the biological effects of diesel exhaust are not due solely to a particle effect, particularly with regard to measures of inflammation and allergic responses in the upper airways. These effects are discussed in Chapter 4 of Part B. The TSD has been revised to include discussion of studies which indicate that extraction with a phospholipid emulsion resembling a major component of lung surfactant showed substantial mutagenic activity, sometimes greater than that observed after extraction with organic solvents (Chapter 5). Chapter 3 of Part B discusses bioavailability and metabolic activation of particle-associated organics. Chapter 5 cites findings of increased lymphocyte DNA adducts in humans occupationally exposed to diesel exhaust, and the occurrence of a specific DNA adduct in diesel exhaust-exposed rats which was not observed in rats exposed to carbon black. This information suggests

that the induction of lung cancer in humans associated with diesel exhaust exposure may occur through a non-threshold genotoxic mechanism.

Chapter 7 of Part B now discusses the question of rat-to-human extrapolation that is raised by the apparent differences in the comparative carcinogenicity of diesel exhaust and carbon black in humans and rats. Also, the new Appendix C of Part B summarizes the limited literature on occupational cancer epidemiology of carbon black exposure, adding a new study which found some increase in risk for all lung cancers and a significantly greater risk for one histological type of lung cancer in carbon-black workers with a relatively high exposure. Appendix C also provides alternative calculations for comparing the lung cancer deaths observed in the carbon black workers of Robertson and Ingalls (1980) to predictions based on risk estimates from the Garshick et al. (1987) cohort study.

As stated in Part B's Chapter 6 and in response to Comment 11, the mechanism of action by which diesel exhaust induces lung tumors in rats is not established. As noted in response to Comment 5, information suggests that the induction of lung cancer in humans associated with diesel exhaust exposure may occur through a non-threshold genotoxic mechanism. This genotoxicity may also contribute to at least part of the rat lung cancer response to diesel exhaust exposure, and it should be noted that genotoxic effects are generally not considered to have a no-effect level. In addition, the proposed overload mechanism includes chronic inflammation and associated production of inflammatory cytokines and increased cell proliferation. As noted in a recent paper by Gaylor and Zheng (1996), (1) a threshold dose is questionable if a carcinogen acts via a cell receptor, (2) even a nongenotoxic carcinogen that increases the cell proliferation rate by augmenting an endogenous mechanism is not likely to have a threshold dose, and (3) dose response curves for cell proliferation and tumor incidence do not necessarily mimic each other.

Finally, the type of overload situation observed at high doses in rats is not thought to have occurred at the levels of diesel exhaust exposure experienced by the human subjects of epidemiologic studies that reported elevated rates of lung cancer.

23. Comment summary: With respect to the genotoxicity of diesel exhaust and the existence of a threshold, the document fails to differentiate between the evidence obtained with the laboratory-prepared extracts of individual exhaust components and the activities of the whole diesel exhaust. In fact, the document disregards published information reporting the lack of the bioavailability of these components in biological fluids and the living organism. The text should recognize that diesel exhaust is not a homogeneous product but a complex mixture that consists of: (a) a vapor phase that contains trace amounts of compounds identified as causal factors responsible for the formation of tumors, and (b) particulate matter that can be separated into additional compartments: (1) an inert carbonaceous core formed by nearly pure elemental carbon, and (2) a small organic fraction adsorbed on the particle surface that is not easily separable (bioavailable) from the particle core by biological fluids, but can be extracted by industrial solvents and that contains traces of compounds classified as carcinogens to humans.
The document should note that when the vapor phase is considered as the potential cause of diesel exhaust-produced tumors, experimental data show that the vapor phase alone (filtered

exhaust) produces no tumors in laboratory rats and the sum of the possible effects of vapor components cannot account for tumors observed in laboratory rats.

A review of certain data suggests that the traditional risk assessment process used by the OEHHA staff failed to consider data that opposed genotoxic mechanisms of diesel particles or had no access to published reports that indicated the inappropriateness of solvent extracts incompatible with the biological environment. (Vostal, pp. 7-11)

Response: The TSD has been revised to include discussion of 1) studies which indicate that extraction with a phospholipid emulsion resembling a major component of lung surfactant showed substantial mutagenic activity, sometimes greater than that observed after extraction with organic solvents (Chapter 5); 2) data indicating that both animal and human occupational exposure to diesel exhaust has been shown to result in the production of urinary metabolites of PAHs and nitroPAHs, indicating bioavailability of those compounds (Chapter 3); 3) studies which show that formation of human lymphocyte DNA adducts is associated with occupational exposure to diesel exhaust (Chapter 5).

The TSD does not posit any particular mechanism as responsible for diesel exhaust carcinogenesis. The presence of retained particles has not been established as the primary tumor-inducing cause in humans. Epidemiologic studies cited in the document and the new meta-analysis of those studies suggest that humans have experienced levels of diesel exhaust exposure that are associated with lung cancer; any hypothesized threshold above those levels seems implausible. Human exposures in these epidemiologic studies were below levels that would be associated with overload in the human lung.

The TSD discusses the composition of diesel exhaust, including the several fractions of diesel exhaust. Studies describing increased lung tumor incidence in mice and increased incidence of splenic malignant lymphomas in rats when exposed to filtered diesel exhaust are discussed in Chapter 6. Studies indicating that the semivolatile phase of diesel exhaust is genotoxic are discussed in Chapter 5. It should be noted that there are PAH and nitroPAH components of the several phases of diesel exhaust which have not been evaluated individually for carcinogenic potency. Also, it is probable that the chemical speciations of diesel exhaust performed to date have not reported every PAH, nitroPAH and related compound present in diesel exhaust.

There are 5 carcinogenic toxic air contaminants present in the gas phase of diesel exhaust (acetaldehyde, benzene, 1,3-butadiene, chlorinated dioxins/dibenzofurans, and formaldehyde) and 25 carcinogenic toxic air contaminants in the semivolatile/particulate phase (Benz[a]anthracene, Benzo[a]pyrene, Benzo[b]fluoranthrene, Benzo[j]fluoranthrene, Benzo[k]fluoranthrene, Chrysene, Dibenz(a,h]acridine, Dibenz[a,j]acridine, Dibenz[a,h]anthracene, Dibenzo[a,e]pyrene, Dibenzo[a,h]pyrene, Dibenzo[a,i]pyrene, Dibenzo[a,i]pyrene, 7H-Dibenzo[c,g]carbazole, 7,12-Dimethylbenz[a]anthracene, 1,6-Dinitropyrene, 1,8-Dinitropyrene, Indeno[1,2,3-cd]pyrene, 3-Methylcholanthrene, 5-Methylchrysene, 5-Nitroacenaphthene, 6-Nitrochrysene, 2-Nitrofluorene, 1-Nitropyrene, and 4-Nitropyrene).

Comments of the American Trucking Associations, Inc.

1. Comment summary: Taken as a whole, available scientific evidence does not support listing of diesel exhaust as a toxic air contaminant (TAC) to the extent proposed in the preliminary TSD. There is significant uncertainty in many of the studies, and their underlying design and methodologies which must be carefully considered. Taken together, these circumstances do not warrant diesel exhaust being listed as a TAC. (Comments dated October 14, 1994, pp. 3, 12)

Response: The June 1994 draft Part B found diesel exhaust to meet the definition of a TAC based on findings of carcinogenicity and the results of the risk assessment. The draft TSD did examine the design and methodologies of the studies and the uncertainties in their results. The document now includes a formal meta-analysis which further evaluates the association of diesel exhaust and cancer in humans.

2. Comment summary: The TAC identification program process should include application of alternative risk assessment methodologies to quantify the effects of highly conservative, policy-driven assumptions incorporated into state-approved risk assessment methodologies. (p. 2)

Response: The commenter does not specify the highly conservative assumptions or the alternative methodologies that should be included. The TSD reports a range of risk based on several methodologies for animals and humans. The central tendencies and the 95% upper confidence limits (UCLs) of the statistical results are presented. The 95% UCLs afford a valuable way to characterize risks to allow public health protection.

3. Comment summary: Many of the issues which appear to most directly influence risk estimates, and for which conclusions can be drawn in the near term, deal with the underlying assumptions in the principal epidemiologic studies used in the risk assessment. However there are many more issues which deserve further analysis. These may include: quantifying ambient exposure; quantifying the validity of using rat data as a surrogate for human exposure; quantifying the influence of a "threshold effect" on carcinogenesis and defining that threshold; and a follow-up study of the Garshick cohort, with emphasis on controlling for confounding factors (e.g., smoking). (pp. 2-3)

Response: The TSD discusses quantification of the ambient exposure in Part A. The discussion of the issues concerning use of rat data for human risk assessment has been expanded in Chapter 7 of Part B. It is unclear how the commenter means for the validity of the rat model to be quantified. Part B's discussion of a possible threshold has been expanded. A reanalysis of the Garshick et al. cohort study is presented in Appendix E of the revised TSD Part B. A follow-up epidemiologic study with emphasis on controlling for confounding factors is likely to be useful for future risk assessments, but is not currently available for incorporation into the revised TSD.

4. Comment summary: Both the Part A and B documents contain numerous requests for additional information, recommendations, or clarification to address recognized uncertainties. The proposed process timeframe should be extended to allow for adequate analysis of these uncertainties. (p. 3)

Response: Both parts of the TSD were released for public comment in 1994. Over two years have passed since then, so there has been enough time for adequate analyses of the uncertainties. Public input has been helpful.

5. Comment summary: The TSD's conclusions must be evaluated for consistency with 1993 amendments to Health and Safety Code Section 39661(c) (SB 1082, Calderon). The law now requires the Scientific Review Panel (SRP) to reject a health effects report if it determines that the report is not based on "sound scientific knowledge, methods, or practices." There is sufficient uncertainty in the TSD to support more thorough exposure and health risk assessment analyses. (p. 3)

Response: OEHHA staff are confident that the health effects document is based on sound scientific knowledge, methods and practices. However, this statutory standard is for the SRP to apply. In preparing the original draft TSD, OEHHA staff considered many uncertainties in data and interpretation. Commenters raised further issues that we have addressed. Thus the new draft is more thorough than the original draft.

6. Comment summary: California's TAC identification process for diesel exhaust should consider and complement work underway at the national and international levels, including work by the Health Effects Institute, the U.S. EPA, NIOSH, and the World Health Organization. (pp. 3-4, 13)

Response: OEHHA staff have considered the work referenced by the commenter. Indeed, we have consulted with investigators at each of the referenced organizations. OEHHA cosponsored a January 1996 technical workshop with all four of the organizations mentioned in the comment. The process leading to
the revised draft has also benefited from a draft report by U.S. EPA (December 1994) and a report by the Health Effects Institute (1995). With regular consultations, we have sought to harmonize our work with that of the U.S. EPA.

7. Comment summary: The emission inventories and health effects studies referenced in the TSD are primarily based on exhaust emissions from outdated fuel formulations, limited-application fuel formulations and outdated engine technology. Given the fact that reformulated fuel and improved engine technology have *significantly reduced* ambient particle concentration in recent years, these innovations will significantly influence both the exposure and unit risk estimates. This point is further emphasized by future planned reductions in diesel engine emissions standards and the control of previously unregulated sources of diesel exhaust emissions. OEHHA should evaluate the effect of reductions in diesel particulates. The commenter expects that the data will show that these improvements significantly reduce the preliminary risk estimates.

The predicted risk estimates must reflect California's most current diesel exhaust emission inventory and the unit risk associated with emissions from significant contributing sources. The TSD's diesel particulate level (and thus exposure and risk) estimates should be reduced by a factor which reflects recent reductions in diesel motor vehicle emissions.

In estimating unit risk, OEHHA has relied heavily on the Garshick study of railroad worker exposure to diesel locomotive exhaust. Diesel locomotive exhaust presumably represents a fraction of the 23% of PM that ARB attributes to "other mobile sources." Locomotive diesel engines are substantially different from other diesel engines, it is clear that diesel locomotives are not the primary source of diesel exhaust PM emissions in California, and the lung cancers identified in the health effects data are a result of particle accumulation in the lung ("particle overload").

Until we have a better understanding of the toxicological effects of different diesel fuel formulations and engine combustion efficiencies, it is grossly premature to assume that risk from diesel exhaust exposure can be accurately characterized by a single emission source. Further analysis may show that diesel locomotive exhaust is not an appropriate surrogate for characterizing risk due to diesel exhaust exposure in California. (pp. 4-5, 7-8)

Response: It is likely that the composition of diesel exhaust does vary somewhat with engine (source) type, year and fuel formulation. Whether these variations importantly impact the risks associated with diesel exhaust cannot be assessed without quantitative speciation of the components of the exhaust at issue and an index of the toxicological concern associated with each of the measured components. Because this information is not available, we have not been able to take into account, in the risk assessment, differences among types of diesel engines, model years, or fuels. The Air Resources Board is sponsoring work to speciate the components of current diesel exhaust.

Part B of the TSD discusses genotoxicity studies which indicate that changes in diesel fuel composition have not been demonstrated to eliminate exhaust genotoxicity, and that changes in engine type and year have a relatively small effect on the magnitude of diesel exhaust genotoxicity (see Chapter,5). The TSD also discusses studies on rats which largely found similar doses of diesel exhaust to have about the same carcinogenic effects even though several different engine types and fuels were used to generate diesel exhaust (see Chapter 6).

Changes in engine design could reduce or heighten the risk associated with a given mass of diesel exhaust particles (e.g., by producing particles of different size).

Part B's unit risk estimates are applied to exposure estimates provided by ARB. The exposure estimates reflect governmental controls and other innovations that have occurred. The exposure estimates are current. The TSD is intended to give an assessment of risks at current levels of exposure. If diesel exhaust is listed by regulation as a toxic air contaminant , ARB will certainly take projected (future) exposure levels into account when considering further control measures. The evaluation suggested in the comment is undertaken during risk characterization, without altering the unit risk estimates.

6. Comment summary: The TSD reaches very different conclusions from a U.S. EPA report that is apparently based on the same research database and estimated national exposure and health risk from diesel exhaust particulates. The reasons for difference must be resolved and the two documents reconciled. Risk levels calculated by EPA are significantly lower than those

calculated by ARB and OEHHA. For example, while apparently based on the same research, the U.S. EPA unit risk factor for diesel particulates is a factor of 18 lower than that used by OEHHA in its risk assessment. The differences between the two documents should, at a minimum, be acknowledged as part of characterization of the range of uncertainty in estimating exposure to diesel exhaust and the health risk posed by that exposure. The commenter strongly recommends performing a formal uncertainty analysis for this. At a minimum, a risk uncertainty range must be calculated and provided to decision-makers along with an analysis of the policy implications of uncertainty. (pp. 6, 8)

Response: OEHHA staff have worked to reconcile the differences referenced in the comment. The current draft of the TSD reports a range of unit risks that is very similar to the range suggested by U.S. EPA's current work. The TSD now includes a more detailed characterization and discussion of uncertainty in the health risk assessment. Since control strategies are not being considered at this time, we have not provided a detailed analysis of the policy implications of uncertainty. However, the range of risk estimates can be used in such an analysis.

9. Comment summary: Adjustment for several factors, in conjunction with the use of the U.S. EPA's diesel particulate unit risk factor, could result in risk that is a factor of approximately 100 less than the TSD's value. The factors that should be considered are indoor-outdoor exposure differences, reductions in vehicle emissions from 1990-1995, and roadside monitoring bias. In addition, the phase-in of planned motor vehicle control measures could reduce unit risk factors 200-fold . (p. 8)

Response: OEHHA staff are continuing to use exposure estimates provided by ARB. We are also continuing to use risk factors from our own analyses. As of this writing, U.S. EPA's risk factor is not final. We have kept abreast of U.S. EPA staff work, and believe that our independent analyses continue to add value to the TSD's risk assessment. The adjustments suggested by the comment would affect risk characterization, but not a unit risk value.

10. Comment summary: The principal author (Dr. Kenneth Crump) of a quantitative diesel exhaust risk assessment prepared for U.S. EPA based on the 1988 Garshick retrospective cohort study concluded that the Garshick study is not adequate to support a quantitative risk assessment. This assessment was unable to detect a quantitative relationship and found reasons to question whether the lung cancer trends described by Garshick et al. were at all related to diesel exhaust. The assessment found that some follow-up of the cohort was inadequate, which itself raises questions about the credibility of the study and whether it should be used in the TSD risk assessment. Dr. Crump's overall conclusion was that OEHHA's reliance on the Garshick study is not scientifically justified. Dr. Garshick himself has directly communicated to OEHHA staff his concern that his railroad worker cohort studies should not be used for quantitative risk assessment. (p. 9)

Response: OEHHA staff have analyzed the 1991 report of the analysis cited in the comment and have had extensive consultations with its principal author, Dr. Crump. Although Dr. Crump has corrected the negative slopes that appeared in the report due to a programming error, he continues to conclude from his further analyses that "the data in the Garshick et al. cohort do not

show any convincing evidence of an association between risk of lung cancer and duration of exposure to diesel exhaust or quantitative measures of diesel exhaust". (Crump,1996a). Appendix E of the revised Part B presents new analyses based on the individual data that were the basis for the study of Garshick et al. (1988) and for the analyses of Dr. Crump. The rationale for basing quantitative risk assessment on Garshick's data is developed in Chapter 7. The issues are further discussed in Appendix F of the current draft of the TSD's Part B.

The finding in the Crump et al. (1991) report that the last years of the follow-up were increasingly incomplete is an important one. The subsequent analysis given in the revised TSD, therefore, omits the last four years of follow-up from consideration.

Since the 1994 publication of the draft TSD, Dr. Garshick has given OEHHA staff helpful suggestions regarding our use of his cohort study (1988) data in quantitative risk assessment. OEHHA staff recently asked Dr. Garshick for assistance in responding to comments such as this one. We asked for his view of the uses to which we have put his data, and we specifically gave him an opportunity to express the opinion, if he held it, that we had misused his data. In response, he reaffirmed his position in a 1994 review letter to OEHHA staff. In that letter, he concluded that "the strength of an assessment of risk depends on the assumptions that go into it. You have made a number of assumptions that yield values of unit risk somewhat greater than animal studies, but lower than others using human epidemiologic data. In the end you have to be satisfied with these assumptions. Perhaps it would be better to use a range of potencies as the background for regulating diesel exhaust since considerable assumptions need to be made to use the current human-based data." The TSD now emphasizes a range of risk estimates, as advocated by Dr. Garshick.

11. Comment summary: The quantitative risk estimates provided in the draft document should be recognized as preliminary estimates only and should not be accepted as predictive of potential human health risk. The commenter suggests this in view of the fact that the uncertainty in the preliminary risk estimates has not been quantified. Certain key assumptions used by OEHHA in deriving its risk estimates are uncertain enough to make the risk estimates speculative. In fact, the true risk to humans from low level diesel exhaust exposure may be very different from the estimated risks and, indeed, could well be zero.

OEHHA should undertake a quantitative uncertainty analysis to address the many technical flaws inherent in the preliminary draft health risk assessment and their expected effect in terms of overstating unit risk estimates. This analysis should address several specific factors. Appropriate statistical tools are available. OEHHA's preliminary analysis should serve as a foundation to better define the uncertainties associated with estimating potential human health risks from diesel exhaust exposure. Precise quantification of these uncertainties is necessary to provide for well-informed decisions concerning future use of the risk estimates in a regulatory context. (pp. 9-10)

Response: A formal uncertainty analysis might show that the true risk could be zero but with very small probability. It would also show that the true risk could exceed the values given in the range of risk. It is possible that the modeled probability plots obtained from the formal process would aid risk managers in some way. However, the benefits to risk managers of such an

analysis would probably be small relative to the resources required to conduct the analysis. OEHHA did not have adequate resources to conduct such an analysis for this document. Specific examples of how such an analysis could be conducted were not provided by the commenter.

12. Comment summary: The epidemiologic data cited in the health risk assessment do not support the conclusion that diesel exhaust is a human carcinogen. The methodologies and assumptions used in the Garshick studies illustrate this point. Garshick calculated exposure estimates based on crude dose-response relationships that are not sufficiently accurate to use as a basis for quantitative risk assessment. Assumptions for shopworker exposure appear to have significantly overstated true risk.

Garshick did not evaluate the confounding effect of cigarette smoking within the retrospective cohort study. Because smoking is a known major risk factor for lung cancer, and was linked synergistically to diesel exhaust in at least one other study, its omission will almost certainly impact the results of this study. If the study was in fact measuring the combined effect of diesel exhaust and cigarette smoking, the estimated unit risk for diesel exhaust will grossly overstate its independent risk. (p. 10)

Response: Regarding whether diesel exhaust is a human carcinogen, the TSD thoroughly evaluates the increased relative risks of lung cancer observed in the epidemiologic studies and their association with diesel exhaust exposure. The TSD points out that the studies of Garshick et al. are suitable for use in risk assessment in spite of uncertainties about historical exposure, among other uncertainties. These uncertainties were discussed on pp. 7-18 and 7-19 of the original draft Part B. With regard to shop workers, recent analyses in Appendix E of the new draft show a trend of risk with exposure, excluding the shop workers. In the cohort study by Garshick et al. (1988), age and calendar year were controlled, though smoking was not directly controlled. An argument against confounding by smoking, undoubtedly the most potent source of possible confounding, is that the study relied on auxiliary information about railroad workers at that time from the Garshick et al. (1987a) case-control study. The case-control study found that smoking adjustment had a negligible effect on risks attributed to diesel exhaust. So the same should hold for the cohort study, the design of which should minimize any smoking effect. Using data from the Garshick et al. (1987) case-control study, the HEI report asserted that the elevated relative risk found in the cohort study could not be explained by cigarette smoking. The comment does not specify the report finding a synergism of smoking and diesel exhaust.

The commenter did not provide support for the assertion that assumptions regarding shopworker exposure significantly overstated true risk. Shopworkers are no longer included in the main analyses of the Garshick et al. (1988) cohort data presented in the TSD's quantitative risk assessment.

13. Comment summary: The commenter supports a conclusion of the American Health Foundation that using commonly established criteria for determining causation, available evidence is insufficient to establish diesel exhaust as a lung carcinogen. (pp. 10-11)

Response: Comment noted.

14. Comment summary: Review of' epidemiological data for carbon black workers suggests that extrapolation of human risk from animal data is not appropriate. Because carbon black and coal dust exposures are frequently used as models for lung particle overloading, the absence of lung cancers in occupationally exposed carbon black and coal workers must be better quantified before one can make a conclusion concerning the health effects of diesel exhaust. The same animal model that showed high concentrations of inhaled diesel particulate to be carcinogenic in rats has also shown that rats inhaling airborne carbon black (with no associated organics) also develop lung tumors at equivalent (or even lower exposure concentrations. The rat data suggest that carbon black and diesel exhaust are of equivalent carcinogenicity and would predict similar cancer potency factors. The validity of the rat-human extrapolation for diesel exhaust can be tested by examining whether the tumorigenicity of carbon black in rats in concordant with lung cancers in workers exposed to carbon black. OEHHA should consider a major report on carbon black epidemiology in this regard. The high lung cancer rates predicted for carbon black workers by the animal data are not substantiated by industry experience, which raises serious doubts concerning the validity of the rat-human extrapolation for diesel exhaust. (p. 11)

Response: OEHHA staff considered the report on carbon black epidemiology referenced in the comment. Appendix C of the revised Part B includes a section on carbon black epidemiology. The commenter has not established that the power of the studies of carbon-black workers or coal workers is sufficient to detect an effect on lung cancer rates even if one were present at the levels predicted for diesel exhaust from human data in the TSD. Appendix C in the new version of the TSD now reviews the carbon-black worker studies and calculates that lung cancer deaths in a cohort of U.S. carbon-black workers may or may not differ substantially from predictions, depending on the assumed historical level of carbon-black exposure and the assumed values of unit risk. Nevertheless, the lack of observation of a significant association of carbon black exposure and lung cancer could simply be due to different mechanisms dominating the high-exposure animal test and the more moderate human exposure. Coal dust would be even more likely to have a different mechanism of action because of the different size and nature of the particle.

15. Comment summary: Available evidence suggests that a threshold exists below which diesel exhaust exposure will not lead to a carcinogenic response. The OEHHA evidence of “genotoxicity and of quantitative analysis of the cancer bioassay" is based on incomplete evaluation of available data.

New evidence shows that, first, the OEHHA assumption of genotoxicity of diesel exhaust inappropriately used extracts obtained by employing industrial solvents as a surrogate of particle action. These conditions do not exist in the living organism and whole diesel particles produce no or minimal mutagenic activity when tested by laboratory assays.

Secondly, long-term animal studies display a clear no-effect level in animals exposed to low concentrations of diesel exhaust. These low concentrations exceed California's preliminary ambient levels by two orders of magnitude. The tumor response in animals exposed to high concentrations of diesel exhaust is explained by a non-genotoxic (epigenetic) action of excessive loads of particles deposited in the lung. The tumors occur whenever lung clearance mechanisms

are overburdened by high levels of fine particles (an "overload"), irrespective of their chemical composition. The soot-associated organic compounds do not contribute to the prevalence of lung neoplasms in the animal assay and do not support the estimation of human lung cancer risk from rat data on the basis of the particle-associated organic compounds. This evidence suggests that there is a threshold below which overloading does not occur.
(pp. 11-12)

Response: The TSD has been revised to discuss 1) studies which indicate that extraction with a phospholipid emulsion resembling a major component of lung surfactant showed substantial mutagenic activity, sometimes greater than that observed after extraction with organic solvents (Chapter 5); 2) data indicating that both animal and human occupational exposure to diesel exhaust has been shown to result in the production of urinary metabolites of PAHs and nitroPAHs, indicating bioavailability of those compounds (Chapter 3); 3) studies which show that formation of human lymphocyte DNA adducts is associated with occupational exposure to diesel exhaust (Chapter 5). This information suggests that the induction of lung cancer in humans associated with diesel exhaust exposure may occur through a non-threshold genotoxic mechanism. This genotoxicity may also contribute to at least part of the rat lung cancer response to diesel exhaust exposure. In addition, the proposed overload mechanism includes chronic inflammation and associated production of inflammatory cytokines and increased cell proliferation. As noted in a recent paper by Gaylor and Zheng (1996), (1) a threshold dose is questionable if a nongenotoxic carcinogen acts via a cell receptor, (2) even a nongenotoxic carcinogen that increases the cell proliferation rate by augmenting an endogenous mechanism is not likely to have a threshold dose, and (3) dose response curves for cell proliferation and tumor incidence do not necessarily mimic each other.

The comment's mention of a no-effect level in certain animal studies does not establish that diesel exhaust-associated carcinogenicity is completely dependent on a threshold-based or non-genotoxic mechanism. One criticism of this inference is that a no observed effect level is not the same thing as a no observable effect level: It is possible that sufficient numbers of animals to observe an effect were not tested. In addition, humans may be more sensitive than the animals to whatever mechanisms may be involved.

Comments of the Association of American Railroads

1. Comment summary: The commenter retained Dr. Robert Reger to scrutinize the findings of Part B of the TSD. Dr. Reger found that: (1) with the exception of eye irritation, the epidemiologic data on the relationship between diesel exposure and health effects are inconclusive and inconsistent; (2) there is no convincing evidence of a link between diesel exhaust exposure and lung cancer; and (3) the study by Garshick et al. cannot, consistent with sound scientific judgment, be relied upon for conclusions about the relationship between lung cancer and the exposure to diesel exhaust of railroad workers because of failure to control for cigarette smoking, questionable categorization of individuals, and unreliable assumptions about exposure.
(Comments dated November 7, 1994, p. 1)

Response: OEHHA staff disagree with each of the points cited here as Dr. Reger's findings. Please see our responses to Dr. Reger's specific comments, below.

2. Comment summary: There is no scientific basis for concluding, as Part B proposes, that there is a link between diesel exhaust exposure and lung cancer. (p. 2)

Response: Part B of the TSD now includes a meta-analysis of the diesel exhaust epidemiology that provides quantitative summaries of the strength of the evidence. Regarding whether diesel exhaust is a human carcinogen, the TSD thoroughly evaluates the increased relative risks of lung cancer observed in the epidemiologic studies and their association with diesel exhaust exposure. A Health Effects Institute report (HEI, 1995, p. 269) has concluded that exposure to diesel exhaust provides the most reasonable explanation" for the elevated rates of lung cancer.

3. Comment summary: In the draft health risk assessment, OEHHA indicates more than once that a high degree of consistency exists linking diesel exhaust emissions and bronchogenic cancer, thus indicating that diesel exhaust exposures cause or contribute to the development of lung cancer. Such a declaration is at odds with other agencies (NIOSH and IARC) that have indicated that diesel exhaust is only a potential or probable human carcinogen. According to OEHHA, a series of (consistent) studies which followed IARC's findings suggests that the classification of diesel exhaust should be stronger than "potential" or "probable." A careful review of the epidemiological literature reveals that this is not true. No subsequent publication has appeared that should alter IARC's conclusions. OEHHA has taken giant leaps of faith to suggest that diesel exhaust causes bronchogenic cancer in humans. An evaluation of mortality studies makes it clear that there is no consistency of results that causally links diesel exhaust and lung cancer.

Of the several epidemiological articles reviewed, none can be taken as positive and as conclusive evidence of a causal relationship between diesel emissions and lung cancer. Although some studies suggest that a small excess risk of lung cancer exists in conjunction with diesel exhaust, sufficient evidence to make a final determination on this issue is not available on actual diesel exhaust exposure and confounding variables such as cigarette smoking. ("Potential Health Effects from Diesel Emissions with Comments on the CalEPA/OEHHA 'Preliminary Draft Health Risk Assessment for Diesel Exhaust' Dated June 1994," by Robert B. Reger, Ph.D., pp. 13-15)

Response: Part B of the TSD now includes a meta-analysis which evaluates the epidemiologic literature's consistency with an association between diesel exhaust exposure and lung cancer. Given the findings of this meta-analysis and the other data presented in the TSD, the relationship between diesel exhaust and lung cancer in humans is consistently supported by the available data.. The statement about a "series of studies" that followed IARC's findings has been deleted. The discussion regarding whether diesel exhaust is a human carcinogen has been extensively revised to be more specific and to reflect the meta-analysis. The TSD's conclusions regarding whether diesel exhaust is a human carcinogen are presented in Chapters 1 and 6 of Part B.

4. Comment summary: Certain work by Wynder and Higgins is instructive on the issue of considering multiple confounding factors in interpreting cancer epidemiology studies. On a

related matter, a review of issues put forth in another publication by Wynder and colleagues would be beneficial. (Reger, p.13)

Response: OEHHA staff considered the printed version of a lecture by Wynder and Higgins (1986). It discusses multiple confounding factors for lung cancer in two studies, Howe et al. (1983) and Hall and Wynder (1984). The major points mentioned are included in the reviews of those studies in the TSD. The article of Wynder et al. (1990) on "wish bias" raises a number of general and well recognized points. The article recommends objectivity in the interpretation of findings and endorses peer review. OEHHA has sought to be objective in its analysis; the Toxic Air Contaminant identification process provides for ample public and scientific peer review to secure the benefit of review by persons with a broad range of perspectives and scientific expertise.

5. Comment summary: On the basis of certain factors involved in considering causation, (1) strength of association and (2) consistency, it would be illogical to imply from the reviewed epidemiological literature a clear cut causal relationship between diesel emissions and lung cancer.

The condition of temporality is thought to be met in the studies reviewed, but the factor of biological gradient (or exposure-response) is highly questionable at best.

The issue of coherence and biologic plausibility for an association between diesel emissions and lung cancer remains debatable. (Reger, pp. 13-15)

Response: Referring to Monson's classification of rate ratios (Monson, RR, Occupational Epidemiology, Boca Raton: CRC Press, Inc. 1985. [The “Second Edition”, 1990 uses the same classification.], the detailed comment does not consider the strength of association to be high. The comment asserts that ,'most of the studies with high(er) risk estimates (i.e. around 1.5) are at least partially flawed to one degree or another." This assertion is puzzling because one of the best controlled and generally well conducted studies, the Garshick et al. (1987a) case-control study had a relative risk of 1.4. This value of risk is in Monson's range of weak association (1.2-1.5), but for such a strong study, would appear not to be likely to be the result of a spurious association, as is the concern of studies with relative risks that are not well above 1.0.

The detailed comment rates the consistency factor as low. The meta-analysis of Appendix D shows a considerable degree of consistency among studies. The comment on temporality agrees with the TSD. The case for an exposure-response relationship has been considerably expanded in the revised Part B, Section 7.2 (quantitative risk assessment) and Appendix E.

The animal data are relevant to coherence. Chronic inhalation studies have consistently demonstrated significant increases in lung tumors in rats exposed to unfiltered diesel exhaust.. IARC (1989) has listed diesel exhaust as a carcinogen based in part on sufficient evidence of carcinogenicity in animals. Tumors at the same contact site (lung) have been observed in association with diesel exhaust in humans. The animal data have not been shown to be mechanistically irrelevant to human cancer risk from diesel exhaust inhalation.

Biologic plausibility of diesel exhaust-induced lung cancer is supported by evidence of bioavailability of genotoxic substances, and is supplemented by postulated epigenetic mechanisms.

The TSD discusses the various criteria for causal inference in Section 6.2. The discussion has been revised and expanded in the new version of the TSD. The TSD thoroughly evaluates the increased relative risks of lung cancer observed in the epidemiologic studies and their association with diesel exhaust exposure.

6. Comment summary: The causation evaluation factor termed "experimental evidence" (this relates to whether or not there is evidence that removal or reduction of exposure provides a preventive effect) cannot be addressed with the studies reviewed. (Reger, p. 15)

Response: We agree. Although the meta-analysis in the current version of the TSD describes increased relative risks of lung cancer in humans, there are no published epidemiological studies demonstrating a reduced relative risk of lung cancer after removal or reduction of exposure to diesel exhaust. For the study of toxic agents, the removal of the exposure is ordinarily the only option available for obtaining experimental evidence. The testing of drugs in clinical trials is the more common situation. In fact several prominent sets of criteria for causality (e.g., Monson - see citation in response to Comment 5) do not list experimental evidence for occupational studies.

The ultimate-stage Armitage-Doll model presented in Appendix E finds risk decreasing with decreasing exposure, albeit with a substantial lag. The property of risk following actual exposure in this way is inherent in any ultimate stage model, including models with one and two stages. This pattern is more extreme than for smoking studies, which show that, after cessation of smoking, the risk does not go up so fast with age. This is a characteristic of a late-stage but not an ultimate-stage carcinogen.

7. Comment summary: The TSD appropriately notes reasons indicating that OEHHA regards animal models as subordinate to human data as a firm basis for risk assessment in man. There can be little disagreement with this notion. (Reger, pp. 15, 2-3)

Response: Comment noted.

8. Comment summary: Regarding non-malignant pulmonary effects from diesel exhaust, the TSD appears selective, possibly inaccurate or at least incomplete. The document’s reference to a study of Reger et al. involves a misinterpretation of the data: the 823 coal miners working above and below ground were matched to coal miners working above and below ground at mines not using diesel equipment underground; they were not matched solely to surface workers. After this misinterpretation, the TSD uses the results from this work as evidence suggesting a deleterious effect. A careful reading of the article reveals that the underground workers who were diesel-exposed did have more symptoms and worse pulmonary function than their matched non-diesel-exposed controls. However, the same phenomenon existed among the surface workers and their controls who had equivalent exposures. Thus, it was stated that factors other than diesel exposure

could be responsible for the results and that available information did allow for the rejection of hypothesis of health equality between matched groups. The TSD's citations of work by Gamble et al. involve serious omissions.

A reviewer of data on non-malignant pulmonary effects and diesel exhaust concluded that diesel exhaust in the mining atmosphere was not revealed as being deleterious to respiratory health, and that elevated symptom levels may be associated with inhalation of mineral dust than with diesel fumes. (Reger, p. 16)

Response: A goal of the TSD is to be as complete and accurate as practicable in discussing all relevant issues, including non-malignant pulmonary effects. responses to the comment's particular points follow.

The TSD's discussion of the Reger et al. (1982) study has been amended to reflect the fact that both above and below-ground control miners were used for comparison with the respective diesel exhaust-exposed miners. A more detailed discussion of the conclusions reached by Reger and colleagues has been added to Part B, Chapter 4.

One of the comment's citations of the work of Gamble et al. is not cited in the TSD; this is from a 1978 proceedings of a symposium, and is expected to be covered by three later (1983) citations of studies on those salt miners. The other four of the comment's citations are referred to in Section 4.1 of the 1994 draft Part B. Although the comment did not provide detail of the claimed serious omissions, the TSD's sections summarizing Gamble et al. have been rewritten and expanded.

In regard to the review of Glenn et al. (1983), two studies have been published since that time indicating possible respiratory problems with diesel exhaust in mining environments. The results of the non-cancer respiratory studies are, however, not consistent.

9. Comment summary: Male railroad workers have been shown to have one of the highest rates of smoking of all occupations. In addition, it is of importance that data from work underway indicate that a tendency exists for workers to under-report their smoking habits, reporting less and less smoking with repeated interviews. Inaccurate and incomplete reporting can have a dramatic effect on a risk ratio in the neighborhood of 1.5. (Reger, pp. 16-17)

Response: In regard to the assertion that railroad workers had a smoking prevalence that was far and away higher than in the general population, some perspective is useful. As stated in the comment, Stellman et al. (1988) reported that 80% of railroad workers admitted having ever been smokers. Those authors also pointed out that their (American Cancer Society) survey was highly selective and that a companion study (Brackbill et al. 1988) actually uses a population sample, which allows direct comparison of subgroup results with the national average. That study by the National Institute of Occupational Safety and Health found that 68.5% of railroad employees admitted having been smokers, compared to national averages for white males: 65% of those employed, 71% of those unemployed, 66% of those not in labor force, and for black males: 62% of those employed, 71% of those unemployed, 56% of those not in the labor force. These results

appear to show that the smoking prevalence for railroad employees generally is near the national average prevalence. The difference of 12.5% between the rates for the railroad workers in the two studies needs some comment. The Stellman et al. study population had a median age of 57. That age is nearer to the age of the railroad workers than is the national average age represented in Brackbill et al., who also provided data showing that smoking prevalence depended strongly on age. Their national average smoking prevalence for ages 45-64 was 76%, much nearer the 80%.prevalence obtained by Stellman et al. for railroad workers. Thus, even though the 80% prevalence may be useful to characterize the Garshick et al. cohort study, that number is not appropriate for national comparisons without regard to age. In regard to the commenter's preliminary results finding that railroad workers may under-report their smoking, that would be expected to be essentially as true for any other group. So such under-reporting would not be expected to affect the comparison to the national average.

10. Comment summary: Nitrogen dioxide is not optimal as a marker of diesel exhaust exposure for epidemiologic studies. Misclassification of workers into exposure categories is likely if the classification is based on job or position. (Reger, p. 17)

Response: The 1994 draft TSD relied on research that used nitrogen dioxide as a surrogate in the historical reconstruction of shopworker exposure to diesel exhaust. Use of nitrogen dioxide in this way is clearly subject to substantial uncertainties but appears to be of value. Because of the reported heterogeneity of the shopworker exposures to diesel exhaust, the current draft TSD excludes shop workers in the main analyses in which exposure to diesel exhaust is estimated; so nitrogen dioxide is no longer used as a surrogate for diesel exhaust. In so far as nitrogen dioxide can be used as a surrogate for diesel exhaust particulate exposure, the commenter's preliminary result that average values (with large variances) of nitrogen dioxide measurements are about the same among job categories would support the idea that shopworkers do not, on average, have an elevated exposure, but instead have, on average, about the same exposure as other exposed workers. This preliminary result is consistent with the two Garshick et al. findings (1987a, 1988) that exclusion of shopworkers from the analysis hardly changed the resulting risks, and is also consistent with the Woskie et al. (1988a,b) measurements, except for the shop workers. Woskie et al. found that exposed shop workers had higher exposures, but many shop workers may have had no exposure to diesel exhaust, thus accounting for shop workers appearing to have, on average, the same exposure as the train workers in the commenter's preliminary study. In regard to the high variance observed resulting in exposure misclassification, see the response to the following comment.

11. Comment summary: The commenter has some concerns regarding the Garshick et al. study and report upon which the TSD's risk assessment is based. These include misclassification of exposure and confounding by asbestos or smoking. In addition, the truncation of the cohort and incomplete follow-up of the remainder of the cohort are of concern. An analysis by Crump raises concerns of possibly severe defects in the Garshick et al. work. Dramatic selection effects must exist in the Garshick et al. data.

Although Garshick et al. performed a "yeoman's effort," their data should not be used as the definitive word on the subject of diesel emissions and lung cancer, as contamination of results by

confounders such as cigarette smoking, cohort selection effects, misclassification of exposure, and other unknown factors could have produced the effects seen. The use of the Garshick et al. cohort data for risk assessment purposes is questionable at best and markedly exceeds the bounds of sound scientific judgment. (Reger, pp. 17-19)

Response: The lack of direct information on smoking for the cohort is certainly of concern. However, the commenter has not shown a serious flaw in using information from the Garshick et al. (1987a) case-control study (conducted in the same general population) to justify the assumption of no difference in smoking effect between the group exposed to diesel exhaust and the unexposed group. Smoking can confound results, as pointed out in the comment, but the study design and analysis here make a dramatic effect unlikely.

Some misclassification by exposure may have occurred in the Garshick et al. (1988) cohort study. But that would make it harder to discern a positive result because random misclassification inherently biases the estimated risk toward the null. In regard to confounding with asbestos exposure, that seems highly unlikely because of the care that the study design and analysis took with that issue, including a special study (Garshick et al. 1987b). In regard to possible multicollinearity, some of the models OEHHA staff have developed for the revised TSD (Appendix E) are less susceptible to this problem.

In regard to the cohort selection and the incomplete follow-up in the later years, the comment does not indicate what effect these factors might have on the estimation of the dependence of risk on exposure. In Appendix E of the revised TSD, the problems of the years of incomplete follow-up are avoided because the analyses simply exclude those years (the last four years) from the analysis. Some of the preferred models in Appendix E do refer cancer rates to the national average, although in a way somewhat different than mentioned by the commenter.

The analyses conducted by OEHHA staff in response to this and similar comments suggest that the Garshick et al. (1988) cohort study data, with careful use and an understanding of uncertainties, are adequate to serve as the basis for a quantitative risk assessment.

OEHHA staff have analyzed the 1991 report of the analysis cited in the comment and have had extensive consultations with its principal author, Dr. Crump. Although Dr. Crump has corrected negative slopes that appeared in the report due to a programming error, he continues to conclude from his further analyses that "the data in the Garshick et al. cohort do not show any convincing evidence of an association between risk of lung cancer and duration of exposure to diesel exhaust or quantitative measures of diesel exhaust" (Crump 1996a). Appendix E of the revised Part B presents new analyses based on the individual data that were the basis for the study of Garshick et al. (1988) and for the analyses of Dr. Crump. The rationale for basing quantitative risk assessment on Garshick's data is developed in Chapter 7. Appendix F is devoted to addressing the issues raised by Dr. Crump.

Comments of John F. Beau

1. Comment summary: The commenter is concerned that the health risk assessment document (Part B of the TSD) appears to be limited to the reasoning of only four members of the Office of Environmental Health Hazard Assessment and three Ph.D.'s from the University of California at Berkeley. The commenter would have more confidence in the document if there had been involvement of the national scientific pool. (Letter, dated October 17, 1994, P. 1)

Response: The diesel exhaust risk assessment report has undergone extensive peer review from outside sources such as the U.S. EPA, NIOSH, consultants to industry, and prominent researchers including the principal investigators in key studies. Both the public comments and the staff responses to them are disseminated in an open process and available to the SRP for review. Because of the full public process built into the toxic air contaminant identification program, we have had extensive review from national and international scientific organizations as well as from the public and industry. Additional comment periods will help ensure that the best available science is used to decide whether or not to identify diesel exhaust as a toxic air contaminant.

Within OEHHA, Part B of the TSD received input and review from many staff members who are not listed as primary authors. This wide in-house review included review by senior staff. It would be inaccurate to say that the document is limited to input from, or the reasoning of, only the primary authors listed.

2. Comment summary: Statistics form the foundation for the results presented in the document. The commenter questions the document's sample sizes, standard deviations, etc. (p. 1)

Response: The human and animal data cited in Part B are verified observations. The document specifies sample sizes and standard deviations or p values where necessary. There should be enough information in the document
and its cited sources to answer the commenter's questions.

3. Comment summary: Results from animal tests only questionably may relate to human exposure. The animals were exposed to concentrations of diesel exhaust 1000-fold in excess of actual practice. Tests on hamsters were negative whereas tests on a certain species of rat were positive. Why not accept the hamster tests? Before costly rules are established without certainty regarding the relationship between diesel exhaust and cancer, more realistic study is required. (p. 1)

Response: It is the practice of toxicology to protect human health using relevant observations in animals and other test systems. Rules to protect health must virtually always be established despite the existence of some uncertainty. While extrapolation over several orders of magnitude of exposure concentration does introduce uncertainty, it does not itself invalidate the usefulness of the observations at high concentrations. Prudent public health practice is to use the most sensitive animal species in estimating risks to human health. In the case of diesel exhaust, data from humans exposed occupationally are available to help guide risk assessment; the use of such

data can make interspecies extrapolation unnecessary. The human occupational exposures were on the order of 10-fold in excess of environmental levels. Results from analyses of animal and human studies constitute the range of risks.

Although investigators have conducted three studies of diesel exhaust inhalation and lung cancer in hamsters (these are described in the TSD), OEHHA staff do not generally consider the hamster to be a useful model for qualitative or quantitative risk assessment of potential human lung carcinogens. In reporting their negative findings with diesel exhaust, Heinrich et al. (1986) pointed out that "contrary to the rat," hamsters have "failed to develop lung tumors ... after inhalation of high concentrations of pure BaP (benzo(a)pyrene] or even cigarette smoke., a well known human carcinogen." Ten years later, the International Agency for Research on Cancer (1996) specifically addressed the relative strengths and weaknesses of the hamster model for different tumor types. IARC, too, noted that there have been no reports of lung tumor development in hamsters due to inhalation of benzo(a)pyrene or cigarette smoke. IARC stated that even with radionuclides it is difficult to induce lung tumors in hamsters, except with intratracheal instillation of polonium-210. Nickel and silica were both negative in hamsters upon inhalation or instillation. Instillations of glass fibers and asbestos have yielded mixed results. The insensitivity of the model indicates that hamster data should not be considered valid predictors of human lung cancer risk. Thus the TSD does not present quantitative risk estimates based on the hamster data.

Comments of the California Trucking Association

1. Comment summary: The TSD proposes that diesel exhaust is a toxic air contaminant, and is limited to a search of supporting literature. The TSD is junk science. Presentations and comments at the September 12, 1994, workshop established that a majority of the underlying assumptions used by ARB and OEHHA are flawed. The TSD does not meet the statutory criteria for labeling diesel exhaust a toxic air contaminant. ARB and OEHHA should revise the Draft Report based on valid scientific data, and not release the TSD to the Scientific Review Panel until after a revised draft is released for comment and a recall workshop is held. (Comments dated November 30, 1994, pp. 1, 5)

Response: The current draft of the TSD is being released for public comment and may be formally submitted for Scientific Review Panel (SRP) review. The previous draft built on a thorough search of the literature and contained substantial analyses of the available data. The current draft contains additional analyses, some prompted by public comments. Some written submittals from the September 12, 1994, workshop are considered as comments in this Part C. The commenter does not provide specifics of how the workshop testimony established that underlying assumptions used by ARB and OEHHA are flawed. The TSD continues to support the assertion that diesel exhaust meets the statutory definition of a toxic air contaminant.

2. Comment summary: The Garshick et al. study relied upon in the TSD to determine cancer risk is fatally flawed and is not a valid epidemiological study. Independent researchers have criticized this study for ignoring the confounding effects of smoking and asbestos, and an independent analysis of the underlying data revealed problems that questioned if lung cancer trends were

related to diesel exposure at all. The Garshick conclusions could not be reproduced or verified, and the study was rejected by the U.S. EPA as "not adequate to support a quantitative risk assessment." Garshick et al. found an increasing risk with exposure to diesel exhaust. Independent analysis requested by the U.S. EPA obtained a decreasing risk with exposure. The independent analysis reported that "it was not possible to develop a model for lung cancer mortality as a function of exposure to diesel exhaust from these data." Three full years later, this independent analysis is not included in the TSD. (pp. 1, 2)

Response: For reasons discussed in Chapter 7 of Part B, Garshick et al. (1988) is considered valid and suitable for use in risk assessment. In this study, age and calendar year were controlled, though smoking was not directly controlled. The argument on smoking, undoubtedly the most potent additional source of possible confounding, centers on the fact that the study relied on auxiliary information about railroad workers at that time from the Garshick et al. (1987a) case-control study. The case-control study found that smoking adjustment had a negligible effect on risks attributed to diesel exhaust. So the same should hold for the cohort study, the design of which should minimize any smoking effect but cannot preclude an effect. Confounding by asbestos is unlikely because exclusion of the shop workers, the group most likely to be affected, has only a negligible effect on trend of risk with diesel exhaust.

In the cohort study, it is unlikely that smoking had a strong effect on the observation of an association of lung cancer with diesel exposure, if smoking and diesel exhaust act independently of each other. Evidence for independence comes from the case-control study, which found virtually no interaction between smoking and diesel exhaust on the same general worker population. The assumption of independence allows estimation of the trend of risk (dose-response slope) without needing to use an unexposed group in the calculation, thereby eliminating the need to characterize differences in the exposed and unexposed populations.

OEHHA staff have analyzed the 1991 report of the analysis cited in the comment and have had extensive consultations with its principal author, Dr. Crump. While the report is dated 1991, it was not released until after the 1994 TSD was completed and was therefore not a part of the literature at that time. Although Dr. Crump has corrected the negative slopes that appeared in the report, he continues to conclude from his further analyses that "the data in the Garshick et al. cohort do not show any convincing evidence of an association between risk of lung cancer and duration of exposure to diesel exhaust or quantitative measures of diesel exhaust" (Crump 1996a). Appendix E of the revised Part B presents new analyses based on the individual data that were the basis for the study of Garshick et al. (1988) and for the analyses of Dr. Crump. The rationale for basing quantitative risk assessment on Garshick's data is developed in Chapter 7. The issues are further discussed in Appendix F of the current draft of the TSD's Part B.

3. Comment summary: The document's "literature search" misrepresents scientific studies. The draft contains numerous examples of incomplete reporting. It asserts evidence that diesel exhaust is carcinogenic in rats
and mice. In reporting on mice data obtained by Heinrich, et al., the TSD overlooks unusual results with NMRI mice and documented uncertainty. The International Agency for Research on Cancer (IARC) points out that the incidence of lung tumors in control groups of such mice could

reach 32%. Furthermore, new studies, completed in time to be included in the draft TSD, show exposed mice and control mice that failed to show statistically significant differences at any exposure. These mice were predisposed to tumors at a rate of 30%.

The Fischer F344 rats used in a key toxicological study, by Mauderly, et al., were also predisposed to tumor induction.

The Takemoto et al. study used C57LB mice and reported unusual control groups. Control problems had to be overlooked to proceed with an analysis. Bad statistical assumptions were necessary to manipulate the data.

A Boffetta et al. study did not report that 20% of its population was eliminated from the analysis. The group that was eliminated produced the highest mortality for cancer.

Response: The TSD characterizes the results of carcinogenicity studies of diesel exhaust in mice as mixed, and the TSD does not calculate an estimate of human cancer risk from mouse tumor data. The TSD has been revised to include discussion of more recent mouse bioassays by Heinrich et al. (1995) and Mauderly et al. (1996). The background lung tumor incidence of the NMRI mice does not affect the use of this strain in the cancer bioassays by Heinrich et al. (1986, 1995). The use of C57BL/6N mice and the study design (including control groups) in the Takemoto et al. (1986) study were in no way remarkable; in fact, the C57BL/6N strain is known to have a low background lung tumor incidence. It should also be noted that the primary statistical flaw of the Takemoto et al. (1986) study, as noted in the TSD and by IARC (1989) is that the original analysis failed to note that the difference in benign and malignant tumors between diesel exhaust-exposed C57BL/6N mice and the corresponding controls was significant at $p < 0.05$. There is scientific consensus that exposure to diesel exhaust induces cancer in rats. Additionally, Fischer 344 rats are not considered to be predisposed to lung tumor induction.

The Boffetta et al. (1988) study pointed out that about 20% of the subjects in the study with known smoking status did not report whether or not they were exposed to diesel exhaust and that the consequence could be a substantial downward bias of relative risk. This point is now included in the review of the study in the revised Part B Section 6.2.

4. Comment summary: The TSD alludes to new studies that are never mentioned. On page 1-4 of Part B, the document states that since IARC findings (in 1989), a series of studies remarkable in their consistency have appeared which provide sufficient evidence...". These new and remarkable studies remain a mystery. They simply do not exist. (p. 2)

Response: The new studies (studies not considered by IARC) were: Garshick et al. (1988), Boffetta et al. (1988), Benhamou et al. (1988), Hayes et al. (1989), Steenland et al. (1990), Burns and Swanson (1991), and Gustavsson et al. (1990). However, the statement about a "series of studies" that followed IARC's findings has been deleted from the chapter.

5. Comment summary: The TSD is biased and distorted, and its health risk assessment is junk science. A lack of objectivity is inherent throughout the document. The TSD relies upon theories

which IARC relied upon before a theory that similar tumors were produced in rats by inhalation of dust was interjected. This theory was substantiated with animal exposure data. After the findings of IARC, additional studies provided rigid scientific proof that tumor induction is unrelated to the chemical carcinogenesis by organic molecules associated with the particles. Carbon black and titanium dioxide tests produced equivalent rat tumors to those predicted for diesel exhaust. (p. 2)

Response: The TSD contains substantial analyses of available data. The findings of tumors in rats exposed to particles other than diesel exhaust does not invalidate the TSD's analyses. The 1994 draft TSD cited the preliminary reports of the experiments in rats which found tumors related to exposures to carbon black. The current draft TSD describes studies by Heinrich et al. (1995) and Nikula et al. (1995) which found comparable rat lung tumor incidence rates after inhalation exposure to diesel exhaust, carbon black or TiO_2- Section 6.1.6 of Part B discusses a hypothesis related to these findings, that chronic inflammation, resulting in macrophage and/or neutrophil-induced oxidative DNA damage, that results in mutations may be mechanistically important in the induction of lung tumors, and that cell proliferation may be mechanistically important to the promotion of lung tumors, in rats exposed to high levels of diesel exhaust by inhalation. OEHHA staff disagree that these studies provide rigid scientific proof that genotoxic organic chemicals on diesel exhaust particles are unrelated to tumor induction.

6. Comment summary: The TSD's opinions are in conflict with the scientific community views on the carcinogenicity of diesel exhaust. IARC found diesel exhaust exposure a "probable" human carcinogen based upon the Garshick et al. study. IARC relied upon evidence that now, after proper analysis by Crump et al., demonstrates a negative association between diesel exhaust and lung cancer. U.S. EPA removed the Garshick study from consideration while ARB/OEHHA chose to exclusively rely on it. Since the research IARC relied upon no longer supports diesel as a probable human carcinogen, the only substantiated conclusion is that diesel does not meet the scientific criteria to be labeled a human carcinogen. (p. 3)

Response: OEHHA staff have analyzed the 1991 report of the analysis cited in the comment and have had extensive consultations with its principal author, Dr. Crump. Although Dr. Crump has corrected the negative slopes that appeared in the report, he continues to conclude from his further analyses that "the data in the Garshick et al. cohort do not show any convincing evidence of an association between risk of lung cancer and duration of exposure to diesel exhaust or quantitative measures of diesel exhaust" (Crump 1996a). Appendix E of the revised Part B presents new analyses based on the individual data that were the basis for the study of Garshick et al. (1988) and for the analyses of Dr. Crump. The rationale for basing quantitative risk assessment on Garshick's data is developed in Chapter 7. The issues are further discussed in Appendix F of the current draft of the TSD's Part B.

IARC (1989, Section 4.3) considered not just one study but five cohort studies and five case-control studies. The IARC classification of diesel exhaust was based on limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in animals. There is no special mention of any one study beyond others being the basis of IARC's findings.

W.H.O. (1996) considered diesel exhaust to be a probable carcinogen after considering recent findings although not the material in Appendix E of Part B of this TSD.

Regarding whether diesel exhaust is a human carcinogen, the TSD thoroughly evaluates the increased relative risks of lung cancer observed in the epidemiologic studies and their association with diesel exhaust exposure.

7. Comment summary: The TSD relies on old studies and ignores all later evidence that shows no relationship between lung cancer and diesel exhaust exposure. (p. 3)

Response: The TSD does not ignore studies that snowed no relationship between lung cancer and diesel exhaust exposure. The TSD now contains a meta-analysis of available epidemiologic studies (including negative studies). This meta-analysis provides quantitative summaries of the strength of the evidence.

8. Comment summary: The scientific community disagrees with the TSD's conclusions of chemical carcinogenesis by organic molecules associated with the particles of diesel exhaust. (p. 3)

Response: The TSD does not conclude that this mechanism is operating. The TSD suggests the mechanism as a possibility.

9. Comment summary: The draft cites studies that did not evaluate diesel exhaust exposure. The studies that did measure exposure to diesel exhaust showed no association between lung cancer and diesel exposure. A cited study found elevated risks of cancer for truck drivers, yet the author of that study did not know how many of the drivers, if any, drove diesel trucks.

Of all the studies provided to support the alleged toxicity of diesel exhaust, no single study completely controlled for the effects of smoking, a known cause of lung cancer. Many simply ignored the effects of smoking and claimed association. The TSD's authors selectively reported studies that supported their premise of a diesel exhaust association with lung cancer. One study cites odds ratios of 1.31 (95% C.I. 1.03-1.67) as adjusted for smoking, but the reported odds ratios were not adjusted for smoking. (p. 3)

Response: The meta-analysis that is now in the TSD considers the truck driver studies as a group and addresses confounding by smoking.

A superscript annotation in Table 6-4 of the 1994 draft Part B erroneously indicated that the crude odds ratio of 1.31 from Boffetta et al. (1990) was adjusted for smoking. We have completely revised the table of epidemiological studies in Chapter 6; it no longer mentions this odds ratio.

10. Comment summary: The TSD cites evidence for a dose-response relationship with respect to diesel exhaust based upon a study that provides no such information. (p. 3)

Response: The reference, in Section 6.2.3 (now Section 6.2.4), to the Howe et al. (1983) study as providing evidence for a dose-response relationship has been removed. This study provided data regarding likelihood of exposure rather than magnitude of exposure.

11. Comment summary: The TSD misrepresents many findings and seriously distorts information. Its authors were not objective in either the literature search or the conclusions. These actions are arbitrary and capricious. (p. 3)

Response: The TSD has been developed and extensively reviewed with the intent of providing a fair and reliable characterization of the potential health risks associated with diesel exhaust exposure. It has undergone extensive peer review from outside sources such as the U.S. EPA, NIOSH, consultants to industry, and prominent researchers including the principal investigators in key studies. The full public process built into the toxic air contaminant identification program has provided extensive review from national and international scientific organizations as well as from the public and industry. Additional comment periods will help ensure that the best available science is used to decide whether or not to identify diesel exhaust as a toxic air contaminant. It is our intent to provide a risk assessment which is based upon sound science and sound process.

12. Comment summary: OEHHA staff found no threshold below which diesel exhaust particles are not hazardous to human health, but all existing studies have shown no effect levels for low exposure to diesel exhaust. Even the animal data of key importance to the OEHHA analysis clearly exhibit a dose-response threshold. One study found a dose of 0.35 mg/m^3 to have demonstrated no lung toxicity or little accumulation of particulates for the lungs; its author (Mauderly) stated that other research and his study appeared to support the hypothesis "that there is a threshold in the relationship between cumulative exposure particle clearance over-load phenomenon and ... there should also be a threshold in the relationship between lung tumor incidence and dose." OEHHA is the first scientific body to find a no threshold effect for diesel exhaust particles. This erroneous finding contradicts U.S. EPA findings and the scientific community. A key study used to make this conclusion, the Garshick et al. study, is faulty and the assumptions extrapolated by OEHHA are not supported by scientific fact. (p. 5)

Response: The TSD does not conclude that a particular mechanism is responsible for diesel exhaust-associated carcinogenesis. The TSD does not identify a threshold dose for this effect, and the available data do not establish that there is a threshold. The TSD has been revised to describe potential mechanisms of rat lung tumor induction as a result of diesel exhaust exposure (Chapter 6), and the uncertainties associated with extrapolating human cancer risk from the rat lung tumor data (Chapter 7). The mechanisms of action by which diesel exhaust is associated with cancer in rats and human studies are not known. The studies thus do not establish a threshold, even at levels where they observe no effect, because of their limited power.. There is in this no contradiction of scientific consensus or the U.S. EPA. OEHHA staff have extensively reanalyzed the Garshick et al. study and continue to find that it is appropriate for use in risk assessment. While OEHHA staff have reviewed and revised analyses in response to extensive and helpful public comment, the assumptions used in the previous risk assessment document were appropriate, if subject to improvement.

13. Comment summary: ARB/OEHHA and the U.S. EPA each spent four years studying the same subject and came to diametrically opposite conclusions. The total disparity of results of the two studies leads to only two conclusions: 1) the science underlying the studies is inexact or spurious, or 2) one of the studies was fudged. In either case, the disparate results negate the reliability of the ARB/OEHHA draft TSD as a scientific document on which to base public policy. Furthermore, the overwhelming testimony of renowned scientists expert in the field of toxicology and epidemiology supports the U.S. EPA study's conclusion. Under the circumstances, ARB has no foundation whatsoever on which to base any conclusions that find diesel smoke to be a hazardous substance that is highly toxic to human beings (toxic air contaminant).

Response: OEHHA staff have worked with U.S. EPA staff to resolve the differences referenced in the comment. The current draft of the TSD reports a range of unit risks that is very similar to the range suggested by U.S. EPA's current work. The approaches of OEHHA and the U.S. EPA in assessing the risks of diesel exhaust are complementary and consistent. OEHHA may be giving somewhat greater emphasis to the epidemiologic data, however. In January 1996, OEHHA co-sponsored an international workshop where renowned experts from industry, academia, and government provided valuable advice with regard to this endeavor. In addition, with regular consultations, we have sought to harmonize our work with that of the U.S. EPA. The current draft of the TSD provides a sufficient basis for finding that diesel exhaust is a toxic air contaminant.

Comments of California Cotton Growers Association

1. Comment summary: All of the information in the draft TSD is based on the "old" formulation of diesel fuel, which has been phased out of use in California. It is also based on older technology engines, which are higher emitters than the newer technology engines. It appears to the commenter that a proposal to deem diesel exhaust a "toxic air contaminant" (TAC) would be inappropriate and scientifically unfounded at this time. The proposal to identify diesel exhaust as a TAC should be reconsidered. New studies should be performed on the reformulated diesel and the new diesel technology that is required by state law. Until such studies are performed, there is no scientifically accurate data from which to base a proclamation that diesel exhaust is a TAC. (Letter from Roger A. Isom, Director of Technical Services, dated September 13, 1994, pp. 1-3)

Response: It is likely that the composition of diesel exhaust does vary somewhat with engine (source) type, year and fuel formulation. Whether these variations importantly impact the risks associated with diesel exhaust cannot be assessed without quantitative speciation of the components of the exhaust at issue and an index of the toxicological concern associated with each of the measured components. Because this information is not available, we have not been able to take into account, in the risk assessment, differences among types of diesel engines, model years, or fuels. The Air Resources Board is sponsoring work to speciate the components of current diesel exhaust, however.

As noted in Part B of the TSD, associations with lung cancer have been observed in occupational groups exposed to exhaust from several different types of engines that used several varieties of

diesel fuel. It would be unreasonable to assume that a new fuel or engine design is safe. It is likely that any differences in health effects may be in degree rather than kind.

Given the possible long latency of lung cancer and the resources available for testing programs, it would be possible to ascertain only many years after the widespread introduction of new fuels or engines (if at all) whether the changes in fuel or engines had altered the human cancer risk. If diesel fuel and engines continue to change frequently, under the line of reasoning in the comment, the identification of diesel exhaust as a Toxic Air Contaminant could thus be put off indefinitely.

2. Comment summary: The draft Part B cites many studies as a basis for a conclusion that diesel exhaust is a TAC. Many of these are old studies, from the 1980's. All of the referenced studies were based on diesel used in the 1980's and older technology engines. New "CARB" diesel is now in use. Has OEHHA considered the effect of the reductions in particulate matter (PM) and nitrogen oxide emissions that ARB estimates will be provided by new fuel and emission standards?

The TSD indicates that the PM portion of diesel exhaust has been associated with most of the mutagenicity of whole diesel exhaust. If the new diesel and engine emission standards lower PM emissions, it should be deduced that the toxic emissions have been reduced and continue to be reduced from diesel exhaust. This claim was supported by OEHHA and ARB testimony presented throughout the public hearing process on reformulated diesel. (pp. 71-2)

Response: Changes in fuel formulation or engine design could reduce or heighten the risk associated with a given mass of diesel exhaust particles. Diesel exhaust particulate matter has been used as a surrogate for measuring exposure to whole diesel exhaust. Exposure to diesel exhaust and risk have been thought to be reduced when measured levels of diesel exhaust particulate matter have declined.

Part B's unit risk estimates are applied to exposure estimates provided by ARB. The exposure estimates reflect government controls and other innovations that have occurred. The exposure estimates are current.

The TSD gives an assessment of risks at current levels of exposure. It provides a dose-response assessment that can be applied to current or future exposures, using the mass of diesel exhaust particles as the measure of exposure. If diesel exhaust is listed by regulation as a toxic air contaminant, ARB will certainly take projected (future) particulate exposure levels into account throughout the process of considering whether to require further control measures.

Comments of Crowley Marine Services, Inc.

1. Comment summary: Part B of the TSD excluded many epidemiological studies as having technical flaws but included the study by Garshick which showed an increased risk of cancer to railroad workers (an odds ratio of 1.41). Dr. Kenneth Crump, a noted epidemiologist, has identified the following deficiencies in the Garshick study: (1) Case follow-up was inadequate.

(2) Control for smoking and exposure to passive cigarette smoke was inadequate. (3) Dr. Crump's own analysis showed that there was no relationship to diesel exposure. (4) It is likely that the Garshick study was measuring a confounding variable other than diesel exhaust.

The best statement that can be made, based on the Garshick and other epidemiological studies, is that if diesel exhaust is, in fact, a carcinogen, it is a weak carcinogen. In the epidemiological studies, smoking is a serious difficulty because it demonstrates a strong association with exposure, with odds ratios of around 30. Methods to correct for smoking may be inadequate and the association reported in the Garshick study may simply be a residual smoking effect. It is also possible that other factors (e.g., diet) may have caused the effect. (Comments dated October 14, 1994, pp. 2-3)

Response: The revised TSD includes a meta-analysis that includes 31 studies, the great bulk of the epidemiological studies of diesel exhaust

OEHHA staff have analyzed the Crump report and have had extensive consultations with Dr. Crump. Dr. Crump has since submitted additional analyses that include corrections of his early calculations of slopes of the relationship of risk to cumulative exposure. Dr. Crump continues to conclude from his corrected analyses that "the data in the Garshick et al. cohort do not show any convincing evidence of an association between risk of lung cancer and duration of exposure to diesel exhaust or quantitative measures of diesel exhaust" (Crump 1996a). The issues are further discussed in Appendix F of the current draft of the TSD's Part B. Appendix E presents new analyses based on the individual data that were the basis for Garshick et al.'s 1988 report. The rationale for basing quantitative risk assessment on Garshick's data is developed in Chapter 7.

Smoking is always a concern in population studies, but the analysis used for the Garshick et al. (1988) cohort study does not appear to be affected (see Section 7.3 of Part B). The meta-analysis mentioned above (Appendix D of Part B) indicates that it is unlikely that the association reported in the Garshick study is simply a residual smoking effect or caused by other factors.

2. Comment summary: Epidemiological data should show an increased risk with increased exposure. Data on exposure is often missing or of poor quality in most retrospective studies. In the Garshick study, exposures were ranked qualitatively based on job category. However, shop workers had less risk than engineers or firemen. One would expect to see the opposite outcome, as shopworkers should have the highest exposures. (p. 3)

Response: As pointed out in the TSD, a substantial proportion of the shopworkers was not exposed to diesel exhaust. The revised TSD shows that, due to their very heterogeneous exposure, the overall risk of shopworkers is most likely to be about the same as for train workers. On this basis, the very small reduction of risk with shop workers removed, as reported in Garshick et al. (1988), is well within the random variation of the data.

3. Comment summary. The most serious difficulties in the TSD arise with the animal data and its interpretation. The document focused on studies by Mauderly which documented excess tumors in exposed rats. The Mauderly rat exposure data serves as one of the most significant inputs into

the risk assessment. If the science is faulty for the animal exposures, the risk assessment becomes suspect. The following are the key points where the Mauderly rat exposure studies are open to question:

(1) The effect is species-specific, occurring only in rats but not in mice, hamsters or guinea pigs. This response in rats appears to be an anomaly. The non-tumorigenic response in mice and hamsters closely resembles what is seen in coal miners' pneumoconiosis, which does not typically progress to cancer. In other words, what happens in rats may not happen in humans.

(2) The tumorigenic effect in rats can be produced by any inert particulate, such as carbon black or titanium dioxide. It was long believed that the chemical carcinogens adsorbed onto the surfaces of the carbonaceous particles in diesel exhaust were responsible for causing the tumors. More recent data is now conclusive that the effect in rats is strictly particle-induced, irrespective of what particles are used. This effect, specific to rats, is termed an "overload mechanism" in toxicological literature.

(3) It is highly probable that a threshold may exist for tumor formation using a particle inhalation/rat model. A numerical value or range of values for such a threshold is not yet available. If it can be shown that a threshold does exist, this would be of considerable importance because ARB must adopt a known threshold in its administrative rules. (p. 3)

Response: The Mauderly et al. (1987) rat cancer bioassay data are used to estimate human cancer risk from rat lung tumor data; so, as suggested in the comment, these data are a key input to the risk assessment. However, these data are not the only tumor data that are key to the risk assessment: the risk estimates derived from human data are probably more relevant than the estimates derived from the rat data. Nevertheless, OEHHA staff do not agree that the science is faulty for the animal exposures.

(1) As stated in Chapter 6 of Part B, the mechanism or mechanisms of action by which diesel exhaust induces lung tumors in rats and humans is not established, so it is not clear whether or not what happens in rats happens in humans. Coal dust does not have the same particle size distribution as diesel exhaust, nor does it have a coating of PAHs and nitro PAHs or an associated semivolatile phase containing a number of carcinogens. Diesel exhaust particles are closer in character, for example in particle size, to carbon black particles than to coal dust. Appendix C of the revised Part B calculates carcinogenic incidence from carbon black assuming it has the same carcinogenic effect as diesel exhaust on the basis of particle mass. The different physical character of coal dust makes it of limited use in testing hypotheses about the whether the effects of diesel exhaust observed in animals can be extrapolated to humans.

Animal studies indicate that diesel exhaust particles by mass are more potent than carbon particles in induction of various pulmonary lesions (Ichinose et al., 1995; Nikula et al., 1995; Ulfvarson et al., 1995). The non-cancer effects of diesel exhaust compared to non-diesel exhaust particles are of a significantly greater magnitude in guinea pigs examined using electron microscopy (Nagai et al., 1996). Diesel exhaust particles also are potent initiators of pulmonary inflammatory and localized immunological responses in humans and mice (Diaz-Sanchez et al.,

1994; Fujimaki et al., 1995). Note also that the results of cancer bioassays of diesel exhaust in mice are mixed, not negative. Therefore, it is apparent that diesel exhaust particles have a number of toxicological properties associated with them that cannot be ascribed merely to their particulate nature, nor to the response of a single species.

Although investigators have conducted three studies of diesel exhaust inhalation and lung cancer in hamsters (these are described in the TSD), OEHHA staff do not generally consider the hamster to be a useful model for qualitative or quantitative risk assessment of potential human lung carcinogens. In reporting their negative findings with diesel exhaust, Heinrich et al. (1996) pointed out that "contrary to the rat," hamsters have "failed to develop lung tumors ... after inhalation of high concentrations of pure BaP [benzo(a)pyrene] or even cigarette smoke, a well known human carcinogen." Ten years later, the International Agency for Research on Cancer (1996) specifically addressed the relative strengths and weaknesses of the hamster model for different tumor types. IARC, too, noted that there have been no reports of lung tumor development in hamsters due to inhalation of benzo(a)pyrene or cigarette smoke. IARC stated that even with radionuclides it is difficult to induce lung tumors in hamsters, except with intratracheal instillation of polonium-210. Nickel and silica were both negative in hamsters upon inhalation or instillation. Instillations of glass fibers and asbestos have yielded mixed results. The insensitivity of the model indicates that hamster data should not be considered valid predictors of human lung cancer risk. Thus the TSD does not present quantitative risk estimates based on the hamster data.

(2) The available data do not rule out carcinogenic effects in rats due to mechanisms in addition to overload and do not demonstrate a threshold. Genotoxicity due to the PAH and nitroPAH content of diesel exhaust may play a role in the induction of lung tumors in rats at lower levels of diesel exhaust. (Chapter 5 of Part B now describes extraction under physiological conditions of mutagens from diesel exhaust.) At high concentrations of particles in the animal experiments the available information does not permit differentiation of which tumors may be due to an overload mechanism and which may be due to some other mechanism.

(3) A genotoxic mechanism would not be expected to have a threshold of action. A particle effect, for example if the surface of a particle serves as a catalyst for a reaction that generates free radicals, could trigger such a mechanism. Regarding nongenotoxic mechanisms, note that the proposed overload mechanism includes inflammation and associated production of inflammatory cytokines and increased cell proliferation. As noted in a recent paper by Gaylor and Zheng (1996), (A) a threshold dose is questionable if a carcinogen acts via a cell receptor, (B) even a nongenotoxic carcinogen that increases the cell proliferation rate by augmenting an endogenous mechanism is not likely to have a threshold dose, and (C) dose response curves for cell proliferation and tumor incidence do not necessarily mimic each other.

4. Comment summary: It is difficult to evaluate the scientific validity of the TSD's risk assessment. However, as in most risk assessments, the extrapolation from massive exposures to very low exposures is subject to considerable error. The extrapolation in this case is by a factor of at least 1000 and is more likely to be 100,000 if the exposure data is adjusted.

The risk assessment is dependent upon the exposure data and the animal model. Both of these inputs suffer from severe deficiencies. It is likely that the animal model is totally unrelated to diesel exhaust and its use in the risk assessment is, therefore, improper. (pp. 3-4)

Response: The uncertainties in the extrapolation and modeling of the animal data contribute to our preference for the risk estimates based upon human data. The ranges of extrapolation were given in Table 7-10 in the 1994 draft TSD. The estimates of the range of extrapolation now take into account the revised state-wide average exposure, as well as the intermittency suggested by the commenter; these are:

(1) for Mauderly et al. rats:

$$3.47\ \mu g/m^3\ *\ 35\ hr\text{-}wk^{-1} / 168\ hr\text{-}wk^{-1} /\ 2.3\ \mu g/m^3 \cong 300$$

(2) for Garshick train workers:

$$50\ \mu g/m^3 * 0.33 * 2.3\ \mu g/m^3 \cong 7$$

These values appear in Table 7-12 of the revised TSD. While the calculations based upon the animal data conform to standard practices, the range of extrapolation for the risks derived from rats does introduce uncertainty. However, this range of extrapolation is not unusual and much less than in some other instances such as methylene chloride, nickel, and perchloroethylene. The human data-based risk estimate with its much smaller range of extrapolation, is preferred in Section 7.6 of the revised TSD, as well as in the 1994 TSD. The range of risk estimates based on the animal data is near the range based on the human data.

Comments of Kenny S. Crump (of ICF Kaiser, Ruston, LA, appearing at the request of Mercedes-Benz)

1. Comment summary: The risk assessment analysis in the TSD based on Garshick et al. data is precisely the type of analysis that U.S. EPA asked a group of investigators (including the commenter as principal investigator) to perform. These investigators studied the data underlying the Garshick et al. (1988) study and reported to U.S. EPA that the Garshick et al. study was not adequate to support a quantitative risk assessment, for the following reasons: (1) a look at the two main analyses of Garshick et al. revealed problems that make it highly questionable as to whether the lung cancer trends they described were related to diesel exposure at all; (2) despite extensive analyses that involved several surrogates for exposure to diesel particulate, several ways of accumulating diesel exposure, and separate consideration of several different subcohorts, the investigators were unable to detect a quantitative relationship between diesel exposure and risk of lung cancer in the cohort; and (3) the follow-up of the cohort was clearly inadequate between 1978 and 1980, the last three years of follow-up. It is evident that a sizable fraction of deaths, including lung cancer deaths, was not reported. Because of this last problem alone, it would be unwise to reach any firm conclusions from this study. Although the problems identified by the U.S. EPA's investigators were not apparent from the published study, the TSD's reliance upon the Garshick et al. study is not scientifically justified. (Comments presented at the September 12, 1994, workshop, pp. 1-5).

.Response: Point (1) is apparently a conclusion that follows from Points (2) and (3); all reflect the report to U.S. EPA described in the comment. OEHHA staff have analyzed the report and have had extensive consultations with its principal investigator, this commenter. The exchanges are summarized in Appendix F of the current draft of the TSD's Part B. The commenter has since submitted additional analyses that include corrections of his early calculations of slopes of the relationship of risk to cumulative exposure. The commenter continues to conclude from his corrected analyses that "the data in the Garshick et al. cohort do not show any convincing evidence of an association between risk of lung cancer and duration of exposure to diesel exhaust or quantitative measures of diesel exhaust" (Crump 1996a). The TSD's rationale for basing quantitative risk assessment on Garshick's data is developed in Chapter 7 and Appendix E. The issues are further discussed in Appendix F. Appendix E presents new analyses based on the individual data that were the basis for Garshick et al.'s 1988 report.

OEHHA staff agree about the incomplete follow-up in Point (3). However, we believe that useful conclusions can be drawn from these data. The revised TSD still finds a significant trend of increasing risk with increasing exposure to diesel exhaust, when the incomplete last years of the follow-up are excluded from the analysis.

2. Comment summary: The U.S. EPA investigators mentioned in Comment 1 did not attempt to assume, as was done in the TSD analysis, that exposures to shop workers were higher in earlier years. If the investigators had tried this approach it is likely that they would have found even less evidence of an association, since lung cancer was not elevated among shop workers. (p. 5)

Response: Comment noted. The revised TSD does not include shopworkers in its main analyses of the Garshick et, al. (1988) cohort data because of the heterogeneity of their exposure.

Comments of the Engine Manufacturers Association (EMA)

1. Comment summary: EMA requests that staffs of the Air Resources Board (ARB) and the Office of Environmental Health Hazard Assessment (OEHHA) conduct an additional public workshop, or reconvene the initial public workshop, on the draft report (the TSD), in the spring of 1995. Given the obvious and significant uncertainties surrounding the relevance of the rat data, and the developing conclusion that the current epidemiological data are not suitable for risk assessment, the basic underpinnings of the TSD are not sound and should be reconsidered, not simply refined, in light of developing scientific commentary. The current scientific data and reasoning, evidenced in part by reports attached to these comments, demonstrate a critical need for an opportunity to revisit the fundamental tenets of the TSD. (Letter from Glen F. Keller, Executive Director, dated October 13, 1994, pp. 1, 5-6)

Response: Decisions regarding further workshops will be made by the Air Resources Board. However, OEHHA co-sponsored a scientific workshop in January 1996 to discuss the underpinnings of diesel exhaust epidemiology. OEHHA staff have reconsidered "the basic underpinnings of the TSD" in light of scientific commentary, including presentations and discussion at the scientific workshop. The document was revised taking this information into account. Public comments on the current draft are encouraged.

2. Comment summary: Due consideration should be given to expected reports, including numerous reports being generated by the leading commentators in the area of diesel toxicology that question the basic foundations upon which the TSD is based. These include reports by the U.S. Environmental Protection Agency (U.S. EPA), the World Health Organization (W.H.O.), the Health Effects Institute, and Dr. Joe L. Mauderly. (pp. 1-2)

Response: OEHHA staff considered those reports in revising the TSD. OEHHA was also a co-convenor of a scientific workshop where many of the issues involved were considered.

3. Comment summary: Exhibit B of these comments, a report prepared by EMA expert Joshua Muscat of the American Health Foundation, critiques the risk assessment portion of the draft report, thoroughly reviews the epidemiological studies and concludes that the available evidence is simply insufficient to establish diesel exhaust as a human carcinogen. This report undermines the ultimate conclusion of the TSD, that diesel exhaust is a human carcinogen. (p. 2) -

.Response: The TSD thoroughly evaluates the increased relative risks of lung cancer observed in the epidemiologic studies and their association with diesel exhaust exposure. The TSD's conclusions regarding whether diesel exhaust is a human carcinogen are presented in Chapters 1 and 6 of Part B. See responses below to specific comments from the commenter's Exhibit B.

4. Comment summary: The conclusion that diesel exhaust is a known human carcinogen is based primarily on risk assessment calculations and extrapolations from Garshick et al. (1988) and Mauderly et al. (1987).. However, the results and relevance of the Garshick study have come under considerable attack from the scientific community,, as demonstrated at the ARB workshop of September 1994, and have been critiqued by the U.S. EPA and the W.H.O. In addition, significant concerns have been raised concerning the applicability to human risk assessment of the data derived in the Mauderly study. Significant in this regard are comments by Drs. Mauderly and Garshick themselves. Most significant is the fact that Dr. Garshick was one of the members of a W.H.O. review group which concluded that there are no quantitative data from the current epidemiological studies suitable for the estimation of human risk. The commenter understands that Dr. Garshick informed an OEHHA staff member that a quantitative risk assessment (QRA) should not be based on data in his study because such data did not include any "dose-response relationship." (pp. 2-5)

Response: Based largely on the report of Crump et al. (1991), the results and relevance of the cohort study of Garshick at al. (1988) were criticized at the September 1994 workshop. On the same basis, the U.S. EPA (.1994) and W.H.O. (1996) decided not to use that Garshick study for quantitative risk assessment. Subsequently, Dr. Crump has corrected the negative slopes that appeared in the report due to a programming error, although he continues to conclude from his further analyses that "the data in the Garshick et al. cohort do not show any convincing evidence of an association between risk of lung cancer and duration of exposure to diesel exhaust or quantitative . measures of diesel exhaust" (Crump 1996a). Appendix E of the revised Part B presents new analyses based on the individual data that were the basis for the study of Garshick et al. (1988) and for the analyses of Dr. Crump. The rationale for basing quantitative risk

assessment on Garshick's data is developed in Chapter 7. The issues are further discussed in Appendix F of the current draft of the TSD's Part B.

Since the 1994 publication of the draft TSD, Dr. Garshick has given OEHHA staff helpful suggestions regarding our use of his cohort study (1988) data in quantitative risk assessment. OEHHA staff recently asked Dr. Garshick for assistance in responding to comments such as this one. We asked for his view of the uses to which we have put his data, and we specifically gave him an opportunity to express the opinion, if he held it, that we had misused his data. In response, he reaffirmed his position in a 1994 review letter to OEHHA staff. In that letter, he concluded that "the strength of an assessment of risk depends on the assumptions that go into it. You have made a number of assumptions that yield values of unit risk somewhat greater than animal studies, but lower than others using human epidemiologic data. In the end you have to be satisfied with these assumptions. Perhaps it would be better to use a range of potencies as the background for regulating diesel exhaust since considerable assumptions need to be made to use the current human-based data." The TSD now emphasizes a range of risk estimates, as advocated by Dr. Garshick. I

The W.H.O. assessment was finalized prior to further OEHHA staff analyses that investigate the impact of various assumptions used in estimating a unit risk. These analyses are summarized in Appendix E of the current TSD. These analyses support the use of the individual Garshick et al. cohort data for quantitative risk assessment.

Staff address Dr. Mauderly's concerns separately here (see responses to comments of Joe L. Mauderly).

5. Comment summary: Dr. Crump has provided reasons that support the seemingly uniform conclusion that the Garshick study is not adequate to support a QRA. He concluded that the TSD's reliance upon the study "is not scientifically justified." This conclusion was echoed in an August 9, 1994, letter to ARB by Dr. Gunter Oberdörster. (p. 5)

Response: OEHHA staff have analyzed the Crump report and have had extensive consultations with Dr. Crump, who has since submitted additional analyses that include corrections of his early calculations of slopes of the relationship of risk to cumulative exposure. A summary of the issues raised by his work and OEHHA's further analyses is found in Appendix F of the current draft of the TSD. The conclusion mentioned in the comment may be "seemingly uniform" because the World Health Organization, the Health Effects Institute, and the U.S. EPA all relied on the uncorrected report of Crump et al. (1991).

6. Comment summary: Concerns with Part B of the TSD, including a misunderstanding of epidemiologic principles in certain sections, misinterpretations of some epidemiologic findings, and incorrect and incomplete reporting of select epidemiologic results, should be addressed. (Exhibit B, "The Health Effects of Exposure to Diesel Engine Exhaust" by Joshua E. Muscat, M.P.H., John Whysner, M.D., Ph.D. and Ernst L. Wynder, M.D., pp. 26-27)

Response: The concerns raised in this general comment are addressed via responses to specific comments below.

7. Comment summary: The following statement in Section 1.3.4 seems self-contradictory: "Since the IARC [International Agency for Research on Cancer] findings, a series of studies remarkable in their consistency have [sic] appeared which provide [sic] sufficient evidence of the need to go further than IARC and USEPA in their classification of diesel exhaust as a probable human carcinogen on the basis of limited evidence of carcinogenicity in humans." It is unknown how remarkably consistent findings are based on limited evidence in humans. (Exhibit B, p. 27)

Response: This language has been eliminated from the TSD.

8. Comment summary: Where the TSD states that "the chances of finding such a consistent response among different occupations and studies are very small," the chances are in fact very high, since men who work in blue-collar occupations with presumptive exposure to diesel exhaust have a higher prevalence of smoking than men in the general population. The consistent findings implicate smoking as the causal factor for lung cancer. Further it is only three studies of railroad workers that are consistent. Studies of truckers are not consistent. The strength of association is weak in all studies. (Exhibit B, pp. 27-28)

Response: Seven epidemiologic studies reported lung cancer deaths as standardized mortality ratios (SMRs in Table 6.4 of the 1994 TSD) with no control for smoking. These studies would be subject to bias due to smoking
rates greater than in the general population. These studies would also be subject to a healthy worker effect tending to counteract any smoking effect. Two of these studies were among the few studies that did not include an increase in lung cancer that was significant statistically. Generally the magnitude of the SMRs were about the same as the risk ratios for the studies that were internally standardized and therefore not very susceptible to bias
due to smoking.

The TSD now includes a formal meta-analysis in Part B that provides a quantitative summary of the diesel-related occupational studies and to help address sources of confounding, including smoking, and consistency and other issues related to the strength of ass6ciation in the epidemiologic studies. As described in Appendix D, significantly elevated risks lacking statistical evidence of heterogeneity were observed for several occupational subgroups, both before and after stratification on whether the individual studies originally adjusted for smoking. In the subset analyses by occupation without regard to smoking four occupational groups gave elevated pooled risk ratios, two of which were statistically significant: truck drivers (pooled RR=1.46, 95% C.I.=1.21-1.61), bus company workers (pooled RR=1.21, 95% C.I.=0.97-1.51), general transportation and professional drivers (pooled RR=1.38, 95% C.I.=1.38, 95% C.I.=1.23-1.55), and railroad workers (random effects pooled RR=1.41, 95% C.I.=1.09-1.86), although the railroad subgroup pooled risk ratio demonstrated evidence of significant heterogeneity. After further stratification for smoking, the pooled risk estimates by occupation in smoking-adjusted studies remained homogeneous, including truck drivers (pooled RR=1.48, 95% C.I.=1.24-1.78), transportation and professional drivers (pooled RR=1.42, 95% C.I.=1.27-1.58), and railroad

workers (pooled RR=1.63, 95% C.I.=1.27-2.09). These findings do not implicate smoking as the causal factor for lung cancer.

9. Comment summary: An analogy presented in Section 1.3.4 of Part B regarding environmental tobacco smoke (ETS) has no meaning. No inference about diesel exhaust can be made from studies of ETS because the association between ETS and lung cancer is controversial. (Exhibit B, p. 28)

Response: The analogy has been removed.

10. Comment summary: Section 6.2.3 discusses criteria for finding causation. Regarding the probability that findings are due to chance, the TSD states that "it is most unlikely that the increased risk demonstrated in a number of studies could be attributed to chance." Many of the studies cited in the document do not test the hypothesis that diesel exhaust is carcinogenic, however. They merely test the association between occupation and lung cancer. Some studies which did gather specific data on reported exposure to diesel exhaust showed no association between lung cancer and diesel exposure. only two studies that had specific exposure information and controlled for smoking found significant relationships, and these were only for long-term exposure. (Exhibit B, pp. 26-29)

Response: The populations in the occupational studies were identified with diesel exhaust because of expectation of such diesel exhaust exposure in those occupations.

The finding of association is a step on the way to demonstrating a probable link to carcinogenesis.

The comment does not specify the studies which gathered exposure information but showed no association. They are not readily identified. Six studies showed some significant increase of risk ratio with duration of exposure: Damber & Larsson (1985), Hayes et al. (1989), Steenland et al. (1990), Garshick et al. (1987), Garshick et al. (1988), and Gustavsson et al. (1990). Such results could be due to smoking, but that possibility seems very unlikely in view of measuring effects against duration of diesel exhaust exposure. (See response to the next comment). The positive findings from even two of the better of these studies may be of public health concern. Positive findings for long-term exposures may be of great public health concern.

11. Comment summary: Regarding the possibility that findings are due to bias: None of 14 studies completely controlled for smoking, and residual confounding cannot be ruled out as a possible cause of weak associations. Precise information on smoking is necessary to statistically control for its confounding effects. This is especially important for weak associations such as between diesel exhaust and lung cancer. Other possible causes of lung cancer that could explain these findings include asbestos exposure and high dietary fat intake. (Exhibit B, p. 29)

Response: As pointed out in the response to the previous comment, smoking could confound the results of studies. For some studies that would be very unlikely. The Garshick et al. case-control study was one that controlled well for smoking and found that smoking had little effect on the

results. The Garshick et al. studies controlled for asbestos and also found little effect.. The meta-analysis in the new Version of the TSD investigates issues of confounding. Staff are not aware of evidence indicating that dietary fat intake is different among study subjects in any of the studies involving diesel exhaust exposure and lung cancer.

12. Comment summary: Another concern, regarding the possibility that findings are due to bias, is response bias (or "wish bias") in case-control studies (persons with cancer may be more likely to attribute the disease to environmental exposure to asbestos or diesel exhaust, rather than to personal habits; healthy controls are less likely to search for possible past exposures). (Exhibit B, p. 29)

Response: response bias is a form of information bias, discussed on page 6-28 of the 1994 Part B. In these occupational studies, exposure is assumed mostly on the basis of job classification, rather than on the basis of an exposure questionnaire subject to "wish bias." We have changed the document's discussion of bias to specifically address this.

13. Comment summary: Consistency of the findings is the hallmark for establishing causation. The TSD states that "there is a considerable degree of consistency in regard to a finding of elevated lung cancer rates in workers *believed to* have been exposed to diesel exhaust. [emphasis added]" Many of these studies do not have information on diesel exhaust or cigarette smoking. Of those which do, the findings are not consistent. In certain instances, the TSD selectively reported positive findings while ignoring negative findings. For example the TSD reports a finding of increased risk for 5 heavy equipment operators who died of lung cancer (RR = 2.6) in the prospective cohort study by Boffetta but does not report the lack of an association in the same study for a larger number of truck drivers (48 deaths). (Exhibit B, pp. 29-30)

Response: Our treatment of these studies generally followed the authors in their identification of diesel exhaust as the target of their occupational studies. This reflects the judgment of the epidemiologists doing the research. The smoking issue is discussed in responses above. The issue of consistency across studies is now treated in the meta-analysis. Regarding the negative finding that was claimed to be omitted from the TSD: Contrary to the claim, the 48 deaths of truck drivers with their statistics indicating non-significant relative risk are reported in the TSD, both in the text (p. 6-24) and in Table 6.4 on page 6-58 under truck drivers.

14. Comment summary: The TSD reports the odds ratio from the case-control study by Boffetta (1.31, 95% C.I. 1.03-1.67) as. adjusted for smoking; it is actually unadjusted. (Exhibit B, p. 30)

Response: A superscript annotation in Table 6-4 of the 1994 draft Part B erroneously indicated that the crude odds ratio of 1.31 from Boffetta et al. (1990) was adjusted for smoking. We have completely revised the table of epidemiological studies in Chapter 6; it no longer mentions this odds ratio.

15. Comment summary: Regarding the strength of the association: Nearly all studies had relative risks ranging from 1.0 to less than 2.0, and weak associations are more likely to be due to confounding or bias than stronger associations. The major concern in these studies is the lack of

control for potential confounders (including smoking, dietary fat intake, and possible asbestos exposure among truck drivers). Cigarette smoking is the major cause of lung cancer. Studies by Hall and Boffetta et al. show that statistical adjustment for smoking is necessary. (Exhibit B, p. 30)

Response: The concern for confounding does increase for decreasing values of relative risk. Confounding bias is discussed on page 6-28 of the 1994 TSD. The meta-analysis in the new TSD (Part B, Appendix D) supports a causal association of risk with diesel exhaust; it reaches overall positive conclusions with some relative risks below 1.5. As pointed out above, a sufficient number of studies are considered to account adequately for smoking.

16. Comment summary: Regarding evidence for a dose-response relationship: Although the TSD concludes otherwise, the Howe data provide no information on a dose-response relationship. Where data for "possibly" exposed and "probably" exposed railroad workers give a significant test for trend, this simply means that the probability of exposure is related to the risk of lung cancer. It does not provide evidence that the risk of lung cancer increases with intensity and duration of exposure.

Also in contrast to a conclusion in the TSD, the test for trend with duration of diesel exposure in the cohort study by Boffetta was not statistically significant despite the large number of lung cancer deaths observed. A dose-response relationship implies an increasing risk with increasing duration of exposure. There was no increased risk of lung cancer associated with up to 15 years of diesel exposure. (Exhibit B, pp. 30-31)

Response: The text of the TSD has been revised in two places to characterize the clear trend found in Howe et al. (1983) as a trend of risk with probability of exposure. The TSD now characterizes Boffetta et al. (1988) as suggestive of a trend of increased relative risk corresponding to increased duration of exposure ($0.05 < p < 0.10$).

17. Comment summary: Regarding temporality of the associations: Earlier studies of lung cancer suffered from inadequate follow-up periods. Most of the more recent studies cited in the TSD had adequate latent periods. The study of Swedish dock workers by Gustafsson may not have accounted for a sufficient latent period; the follow-up study by Emmelin showed that the smoking prevalence was higher in the lung cancer cases than in the controls, indicating that smoking may have been the cause of the elevated rate of lung cancer. (Exhibit B, p. 31)

Response: The meta-analysis reported in the new draft TSD addresses the sufficiency of latency periods in diesel exhaust epidemiology. As described in Appendix D, latency period was a criterion for excluding or including studies in the analysis. Many studies, several of which showed statistically significant associations between diesel exhaust and lung cancer without being included in a meta-analysis, clearly had sufficient latency periods to be included in the analysis. The latency period in Gustafsson et al. (1986) is not clear, but this study was included in the analysis because what we know about the time course of dieselization makes it reasonable to assume that the workers in that study were exposed to diesel exhaust for long enough so that observed cancer could plausibly be related to the exposure.

As regards the effect of smoking on lung cancer rates, Emmelin et al. (1993, Table 5) did find that smokers had higher odds ratios than nonsmokers for each category of time exposed, as would be expected, regardless of the prevalence of smoking. But the point for checking association of diesel exhaust with risk above that of smoking is the increase of odds ratio with time exposed: This was very clear for the modest number of smokers and less clear for the very small number of nonsmokers.

18. Comment summary: Regarding biological plausibility: Diesel exhaust contains known carcinogens and is carcinogenic in animal models. Only extremely high doses of whole diesel exhaust can induce lung tumors in rodents. Lower doses have not produced cancer. It is unclear whether quantitative risk assessments are valid since in lung carcinogenesis, cigarette smoke particulates cannot induce damage to bronchial epithelium when the lung's ciliated mucus-producing epithelium is intact. Toxic overload of the body's natural self-defense systems may be necessary to induce pathogenesis. In laboratory studies, rats have only developed glandular lung cancer after massive exposure to diesel engine exhaust which caused destruction of defensive pulmonary mechanisms. These cancers may have arisen from the subsequent inflammatory response and not diesel exhaust particulates. Recent rat studies found similar incidences of lung tumors in groups exposed to carbon black or to diesel exhaust, suggesting that particle overload, not the organic fraction of soot, induced these tumors. Inflammation caused by overloading the lung may result in cell proliferation. Humans are not exposed to the levels of diesel emissions which cause this inflammatory process. It is reasonable to assume that particle overloading may be necessary to induce carcinogenesis in humans. The only epidemiologic studies which suggest an increased lung cancer risk were of workers exposed to diesel exhaust for at least 20 years. This appears to support the mechanistic hypothesis of particle overload. Only very large amounts of exposure may induce cancer in humans. (Exhibit B, p. 31)

Response: As stated in Part B's Chapter 6, the mechanism of action by which diesel exhaust induces lung tumors in rats is not established. One proposed mechanism is that exposure to diesel exhaust particulate matter at high concentrations exceeds pulmonary clearance capabilities and causes chronic inflammation. This inflammation leads to macrophage and/or neutrophil-induced oxidative DNA damage resulting in mutations which are instrumental in the induction of lung tumors, and also to cell proliferation which may be mechanistically important to the promotion of the rat lung tumors. This mechanism may have an exposure threshold of action, suggesting that tumor induction due to this mechanism would also have a threshold. Although no mechanism has been established to account for the increased rates of lung tumors in diesel exhaust-exposed workers, Part B of the TSD has been revised to include descriptions of studies indicating that human occupational exposure to diesel exhaust is associated with increased levels of nitroPAH metabolites (Chapter 3) and DNA adducts (Chapter 5) as well as with increased lung cancer incidence. These data support the potential hypothesis that DNA damage resulting from exposure to genotoxic components of diesel exhaust (including the semivolatile phase) results in the induction of lung cancer in humans. This mechanism would not be expected to have a threshold of action. Under these circumstances, inflammation induction may not be mechanistically necessary for the appearance of lung cancer. Additionally, the proposed mechanism that exposure to diesel exhaust particulate matter at high concentrations exceeds pulmonary clearance capabilities and causes chronic inflammation includes the production of

inflammatory cytokines and an increase in cell proliferation. As noted in a recent paper by Gaylor and Zheng (1996), (1) a threshold dose is questionable if a carcinogen acts via a cell receptor, (2) even a nongenotoxic carcinogen that increases the cell proliferation rate by augmenting an endogenous mechanism is not likely to have a threshold dose, and (3) dose response curves for cell proliferation and tumor incidence do not necessarily mimic each other.

The 20 or more years of exposure found to be associated with cancer in workers may not have been sufficiently intense to have been associated with the overload mechanism postulated by the commenter. The general public is exposed for considerably more than 20 years. If duration is important this is a reason to think that lung cancer risk from ambient exposure is biologically plausible and a reason to be concerned about diesel exhaust exposure of the general public.

19. Comment summary: The TSD's statement that "the epidemiologic studies concerning lung cancer risk and exposure to diesel exhaust provide evidence for a causal relationship" must be qualified in light of considerations raised in comments above.

Two studies of the same cohort are insufficient to establish causality. The most important criterion for causality requires consistent findings in different populations. (Exhibit B, p. 32)

Response: Regarding whether diesel exhaust is a human carcinogen, the TSD thoroughly evaluates the increased relative risks of lung cancer observed in the epidemiologic studies and their association with diesel exhaust exposure. The two Garshick et al. studies are not of the same cohort, though the case-control study of deaths in 1982 probably did have some workers who lived past the cut-off date of the cohort follow-up (1980).

20. Comment summary: The railroad findings cannot be generalized to other occupational cohorts such as truck drivers or dock workers. It is important to distinguish between occupational groups when assessing causation. Since more people are exposed to diesel emissions from trucks than from railroad locomotives, particulate emissions from trucks tend to be lower than from railroads. Therefore, the health consequences associated with railroad work may be different that those associated with driving diesel trucks. (Exhibit B, p. 32)

Response: Throughout, the TSD uses inhaled particle mass per cubic meter of air as the sole surrogate for diesel exposure concentration, as explained in Section 7.1. There is likely to be some variation in effect from the same concentration from different sources of emission. There do not appear to be any data available on how to account for effects from different sources. Hence the effect is generalized for a given exposure, as defined, across occupation and environment. If one source produces a higher exposure than another, then the higher exposure will generally lead to a higher risk being expected.

21. Comment summary: Regarding diesel exhaust and human bladder cancer: of 18 studies, nine were negative and eight were inconclusive. The only positive evidence comes from a study of truckers, and it cannot be ruled out that the relationship found in this study reflects poor dietary and lifestyle habits of truckers (including prolonged urine retention). The TSD states that "since bladder cancer is rarer than lung cancer," it is "not a critical issue in risk assessment terms." If the

epidemiologic studies were largely positive with regard to associations between diesel exhaust and bladder cancers, would the results be ignored? Bladder cancer is the sixth leading cause of cancer in the U.S. The TSD's statement is inconsistent with its devoting a whole section to less serious non-cancer health effects of diesel exposure. (Exhibit B, pp. 42-43)

Response: We have revised the statement and this section of the draft document to justify not considering bladder cancers in the quantitative risk assessment. The document indicates that there is a clearer indication for lung cancer and a stronger measure of effect.

22. Comment summary: The TSD's risk assessment (using the Garshick et al. data) leads to a very large uncertainty based upon the use of a linear model at all recalculated estimates of human doses. This uncertainty could be decreased by the use of either the U.S. EPA's default model or a threshold dose model, both of which take into account the sublinear dose-response data from human and animal studies. The use of the linearized multistage model, as used by U.S. EPA staff, accounts in some degree for the sublinearity at low doses. Based on the likely possibility that a threshold dose model may also predict human risks, the linearized multistage model would be an upper estimate of the risks. (Exhibit B, pp. 45-46)

Response: The data used in the 1994 TSD were relative risks from Garshick et al. (1988).. Those data appear to show a sublinear dose-response, reminiscent of the strong finding in the Mauderly et al. (1987) rat data. However, the trend in Garshick et al. (1988) is not statistically distinguishable from linearity. In the new draft TSD, the figure that displays the trend shows the large error bars on the points, in agreement with the results of formal statistical test. The highest exposure point, which shows the steepest rise has the largest error bar. A simple linear relationship appears to be the most reasonable choice at present for humans, with no real indication of sublinearity. If the actual relationship were sublinear, then the present linear approximation would tend to overstate the risk somewhat.

23. Comment summary: The unit risk proposed in the TSD suffers from large uncertainty because the dose-response sublinearities demonstrated in the human and animal studies are not included. The U.S. EPA has partially taken this factor into account, resulting in a unit risk that is 10-fold less than the proposed unit risk in the TSD. The use of the U.S. EPA's unit risk or the use of a threshold dose based upon animal data would decrease the uncertainty for human exposures and provide a more realistic estimate of risks. (Exhibit B, p. 46)

Response: The rat exposures equivalent to those of railroad workers are well within the range of the essentially linear portion of the 95% UCL response characteristic for the rat. So with the TSD’s sublinear analyses of the rat data as a guide, the human risk would be expected to be linear, albeit with a 10-fold higher slope, and thus a sublinear response would not be expected. The range of risk in the TSD has included the 10-fold lower rat results which U.S. EPA relied on in their 1994 Health Assessment Document for Diesel Exhaust. The OEHHA range in the new TSD is expected to be in harmony with the forthcoming USEPA range. However, use of this range does not decrease uncertainty. Rather, use of this range characterizes uncertainty.

24. Comment summary: The epidemiologic data show that there is extreme linearity at low doses or that there is a threshold dose. The animal data from studies by Mauderly et al. and Ishinishi et al. clearly exhibit either a sublinear dose-response or a threshold. Based upon these data and studies that have suggested that there is a large influence of epigenetic mechanisms in diesel exhaust lung carcinogenesis, a risk for lifetime exposure to diesel exhaust would not be predicted at or below 2 mg/m^3 16 h/day, 6 days/week. (Exhibit B, p. 45)

Response: By extreme linearity the commenter evidently refers to the linear portion of the curve of low risk at low exposures, obtained in the TSD for the rat studies, in comparison to the curve of high risks at high exposures (sublinearity). The models used in the TSD are designed to obtain an upper confidence limit on the slope of that linear portion of the relationship at low exposure, even though epigenetic or other processes may be occurring at the higher exposures. The data do not dictate the finding of a threshold.

25. Comment summary: An unpublished reanalysis by Dr. Kenneth Crump suggests that the Garshick data do not provide a reliable basis for determining risk assessment to diesel exhaust. The findings by Crump show no increased risk of lung cancer associated with diesel engine exhaust. The original data published by Garshick should also be questioned since the estimates were unadjusted for cigarette smoking' (Exhibit B, p. 46)

Response: Dr. Crump has corrected the negative slopes that appeared in the analysis due to a programming error, although he continues to conclude from his further analyses that "the data in the Garshick et al. cohort do not show any convincing evidence of an association between risk of lung cancer and duration of exposure to diesel exhaust or quantitative measures of diesel exhaust" (Crump 1996a). Appendix E of the revised Part B presents new analyses based on the individual data that were the basis for the study of Garshick et al. (1988) and for the analyses of Dr. Crump. The rationale for basing quantitative risk assessment on Garshick's data is developed in Chapter 7. The issues are further discussed in Appendix F of the current draft of the TSD's Part B.

Adjustment for smoking in the closely related case-control study (Garshick et al. 1987a) made only a negligible difference in the results, and it is reasonable to assume that would be the case for the cohort study (Garshick et al. 1988).

26. Comment summary: The TSD proposes to list "diesel exhaust" as a toxic air contaminant (TAC). As long as diesel engines remain in operation there will always be diesel exhaust. The constituents of diesel exhaust can vary greatly. In fact, the mixture called diesel exhaust has changed quite dramatically over the past three decades. The TSD should be revised so that it identifies and proposes to list the specific components of diesel exhaust that ARB and OEHHA allege to be TACs.

It might be argued by some that "air" in a nonattainment area on certain days could be a TAC. Yet listing air as a TAC would make little sense. Air is different in different places, depending on its specific makeup. "Air" cannot be regulated effectively. The same analogy applies to "potable

water." Water is not the regulated substance. Rather it is the specific components that potentially pollute water that are the subject of the applicable regulations.

There is no fixed substance known as "diesel exhaust" that can be subject to regulation. Listing diesel exhaust as a TAC would be of little or no value to regulators or the regulated community. Regulators would be faced with the choice of banning the operation of diesel engines in California (which obviously is neither reasonable nor acceptable) or redoing the TAC identification process to determine which, if any, of the constituents of diesel exhaust should be the target of regulation. Similarly, engine manufacturers faced with a TAC listing of "diesel exhaust" would have no idea how to respond.

TAC listings for complex mixtures such as diesel exhaust are both redundant and likely to lead to absurd results. If listing a component of a mixture is otherwise warranted, there is no reason also to list the mixture containing the component. Every mixture containing the component would have to be listed. In this case, if diesel exhaust were listed as a TAC because it contains some targeted component, then there would be no logical reason not to list "air" as a TAC once it was established that diesel exhaust was in air. (Supplemental comments letter from Glen F. Keller, Executive Director, dated November 29, 1994, pp. 1-3)

Response: OEHHA staff understand that the constituents of diesel exhaust can vary greatly. We also understand that identifying specific components of diesel exhaust in particular as toxic could contribute to efforts to make diesel exhaust safer. Yet whether the variations in diesel exhaust importantly impact the risks associated with diesel exhaust cannot be assessed without quantitative speciation of the components of the exhaust at issue and an index of the toxicological concern associated with each of the measured components. Because this information is not available, we have not been able to take into account, in the risk assessment, differences among different types of diesel engines, model years, or fuels. The Air Resources Board staff is sponsoring work to speciate the components of current diesel exhaust. The studies on the biological effects of diesel exhaust that OEHHA staff have considered for the TSD do not provide sufficient data to separately identify or rule out specific components of diesel exhaust particles as toxic air contaminants.

The TSD is intended to give an assessment of risks at current levels of exposure, and a dose-response assessment that can be applied to current or future exposures, using the mass of diesel exhaust particles as the measure of exposure.

Where the comment makes analogies to "air" and "potable water" it appears to confuse contaminants with media. Although diesel exhaust is composed of several substances that are themselves contaminants of air (the medium of exposure), diesel exhaust is, considered as a whole, a contaminant of air. The TSD's risk assessment addresses the toxicity of the particulate portion of that contamination.

Several gaseous components of diesel exhaust are subjects of separate TAC Program proceedings. The Air Resources Board will consider the proceedings' overlap when considering control strategies for diesel exhaust.

OEHHA staff recognize the commenter's concern regarding the potential implications of listing a component of several mixtures as a toxic air contaminant, and the ARB will consider this information in its evaluation.

Comments of Ford Motor Company

1. Comment summary: The commenter compliments OEHHA for thorough listing and discussion of scientific unknowns associated with health risk assessment of diesel exhaust. Part B of the TSD is commendable for specifically listing, and inviting comments on, issues which its authors regard as especially likely to invite criticism. (Letter from Kelly M. Brown, Director, Automotive Emissions and Fuel Economy Office, Environmental and Safety Engineering Staff, dated September 23, 1994, p. 1, and comments, p. 2)

Response: Comment noted. 1

2. Comment summary: Part B of the TSD confuses whole diesel exhaust with the particulate fraction of diesel exhaust. The OEHHA conclusions are actually for particles rather than for whole diesel exhaust. The evidence suggests that any other particles in the same size range would elicit the same effects at the same concentrations as those observed with diesel exhaust particles.

In the animal inhalation experiments and the epidemiological studies, exposure to diesel exhaust is quantified in terms of mass of particles per volume of air, even though the actual exposure was to whole unfiltered exhaust. The OEHHA risk assessment is actually for particles, rather than whole diesel exhaust. The TSD should avoid using the term "diesel exhaust" as a synonym for the particulate fraction of diesel exhaust.

In several places (e.g., p. 7-18) Part B of the TSD notes that "respirable particles contain many of the carcinogenic components of diesel exhaust." However, there are no data as to the contribution of the organic compounds to the rat lung tumor incidence. The discussions of human cancer are all discussed in terms of particle concentration as the measure of exposure. Thus the term "carcinogenic components" of diesel exhaust is undefined, and therefore its use should be avoided. (Letter, pp. 1-2, and comments, p. 1)

Response: The TSD is intended to present a risk assessment that uses the mass of diesel exhaust particles as the measure of exposure. This exposure measure is a surrogate for whole diesel exhaust, however. Thus, the TSD's risk estimates are for whole diesel exhaust. This should be more clear in the current version of the document.

The TSD is not a risk assessment for particles in general, or for all particles of a particular size range. As suggested by the comment, it is difficult to distinguish from the available data between carcinogenic effects of particles and carcinogenic effects of compounds attached to the particles or in the vapor phase of diesel exhaust. The use of the term "carcinogenic components" is not intended to imply that any specific components have been identified as causes of diesel exhaust-associated carcinogenesis. It only means that, individually, these substances have been shown to cause cancer.

3. Comment summary: Of the 18 epidemiology studies cited in the report (Part B of the TSD) as claiming to observe elevated incidences of lung cancer among the "exposed" populations, only two - - those by Garshick et al. can be plausibly interpreted as evidence for a link between lung cancer incidence and occupations in which workers may have been exposed to railway diesel locomotive exhaust. The strength of the conclusion is undermined by confounding factors (primarily cigarette smoking) and the lack of direct measurements of diesel exhaust exposure. In 12 of the 18 studies, the increases in lung cancer incidence were not statistically significant. Except for the two Garshick et al. studies, none of the study designs permitted a test of the hypothesis that diesel exhaust was the cause of the elevated incidence. The report is misleading in claiming there is "remarkable consistency" among epidemiological studies. (Letter, p.2, and comments, pp. 2-3)

Response: Part B's conclusions regarding the consistency of the worker studies have been modified somewhat. Chapters 1 and 6 now note that there is a considerable degree of consistency in finding elevated, although not always statistically significant, lung cancer risks in workers potentially exposed to diesel exhaust within several industries. The meta-analysis now included in the TSD (as Appendix D) supports this statement and also addresses potential confounding factors. In addition, the meta-analysis evaluates the consistency among several studies regarding lung cancer incidence and occupations involving exposure to diesel exhaust.

4. Comment summary: None of the epidemiological studies was supported by measurements of diesel exhaust concentrations in the work place in which the study populations were exposed. Thus exposure to diesel exhaust had to be inferred indirectly. In no case could airborne particles or other pollutants be apportioned to diesel particles. Although several of the studies purported to have corrected for cigarette smokers, the methods by which the corrections were made were not rigorous. The accuracy of the historical reconstructions of the exposure concentrations used by OEHHA to derive a unit risk factor based on the Garshick epidemiological data is unknown. Thus the uncertainties of the resulting unit-risk factor are unknown, and correspondingly it is very difficult to justify technically how OEHHA can propose a unit risk factor based on epidemiological data. When relative risks are less than 2, as they were in the Garshick studies, limitations such as confounding from cigarette smoking and the lack of direct exposure measurements make the conclusions highly uncertain.

Garshick and coworkers (Woskie et al. 1988) attempted to reconstruct plausible estimates of diesel exhaust exposure experienced by the various categories of workers in their epidemiological studies by conducting measurements of particle concentrations under current (mid 1980s at the time of the study) working conditions. These "current" measurements were then used to reconstruct historical exposures. The weakness of this reconstruction was the limited data upon which to estimate historical exposures from current exposures. Moreover, the "current" measurements were of respirable particles less than 3.5 μm diameter, but there are many sources of small particles and the specific contribution from diesel exhaust particles was not determined. As summarized in the report, urban particles are due to numerous sources, including vehicle emissions, roadway dust, meat cooking, etc.

The report acknowledges the limitations of the historical reconstructions, but ignores these limitations and conducts its risk calculation using the historical reconstructions. There is no way of knowing if the historical reconstructions have any connection with actual exposures experienced by the population represented in the epidemiological studies. The exposure estimates are a plausible guess, but no more than that. Moreover, the reconstructions do not permit an estimate of exposures to diesel particles, but only to total particles in the size range less than 3.5 microns. There are many other sources of particles in this size range besides diesel exhaust.

The report should be expanded to include a detailed discussion of the technical basis for how it was possible for OEHHA to accept the results of the risk calculation based on the human epidemiological data. The limitations of the exposure estimates upon which the risk calculation is based are widely known and accepted in the scientific community. Without a better technical justification, the unit risk factor presented in the report can only be described as a guess. (Letter, pp. 1, 2, and comments, pp. 3, 4)

Response: The second paragraph of this comment recognizes that measurements of exposure of railroad workers to diesel exhaust were available. The reason for the comment that the corrections for cigarette smoking were not rigorous is not specified. OEHHA staff find that the rigor of the corrections, when made, is adequate.

The uncertainties of the historical reconstruction of exposures for the Garshick et al. (1987a., 1988) can be somewhat quantitatively characterized. Average exposure measurements made at the end of the study are unlikely to deviate up or down more than 50% from the actual average for the workers of the study at that time. The specific contribution of exposure to respirable particles of diesel exhaust is estimated in Chapter 7 of the TSD Part B. Estimates of the diesel-exhaust portion of respirable particles (less than 3.5 microns diameter) are obtained by subtracting the background level of respirable particles (the exposure level of clerks and signalmen) from the measurement for each of the other job groups. This surrogate for diesel exhaust exposure is used in estimating risk from all components of the exhaust. For the reconstruction, the ramp exposure pattern, defined in Appendix E of the current draft Part B, is very likely to be a lower bound on concentration because concentration from 1959 on, when dieselization was complete, was very unlikely to be less than the measured values at the end of the study because of the introduction of progressively cleaner burning engines. The peak pattern, which has a 3-higher concentration at the inferred peak concentration in 1959 than at the end of the study furnishes a high value of exposure, though not necessarily an upper bound. These uncertainties in exposure estimation are not unduly large. The actual exposure pattern is most likely not to deviate more than 2-fold up or down from the peak pattern of Section 7.3 in the current draft Part B, based on the scattered measurements available.

When relative risks are less than 2, as they were in the Garshick studies, special caution may be needed with regard to potential confounding. One way of addressing this need was the test for smoking effect performed in the Garshick et al. (1987a) case-control study. Another was the attention given to the exposure-response relationship, especially tests of the effect of omitting the background (unexposed) group. The success of these tests lends support to the validity of the positive exposure-response trend found in the quantitative risk assessment.

5. Comment summary: Much more extensive technical justification must be presented to explain how it was possible for OEHHA to reach the conclusions in the draft assessment despite the many scientific unknowns and absence of exposure data. Considering the many gaps in knowledge underlying cancer risk-assessments, it would appear to be scientifically indefensible to promulgate a unit risk factor for any purpose other than possibly setting priorities for future research. To this end, the unit risk factor derived by OEHHA from the interpretation of the animal studies would suggest that cancer risk from diesel exhaust is very small and ought to warrant very low priority as a cancer risk agent. The unit risk factor from the human epidemiological studies is too uncertain for use in any regulatory purpose or in setting research priorities. (Letter, p. 2, and comments, pp. 4-5)

Response: The TSD has been extensively updated and revised in response to comments. It more thoroughly evaluates the evidence and better characterizes the associated uncertainties. These analyses have generally been found to support and elaborate upon the earlier findings. However, the TSD now presents a range of 95% upper bound unit risk factors based upon animal and human data. This range gives a clearer sense of the potential magnitude of the risks. These additions include information on lymphocyte DNA adducts in humans occupationally exposed to diesel exhaust. As pointed out in the response to Comment 4, the TSD's discussion of the exposure reconstruction, the extensive reanalyses from the individual Garshick et al. (1988) data, and the tests for lack of confounding have all added support to the epidemiological analyses. Although the document acknowledges many scientific unknowns including gaps in exposure data, the TSD provides sufficient support for its conclusions. OEHHA staff believe the animal data are useful for purposes of characterizing the magnitude of the potential cancer risk to humans as well as for setting priorities for future research. The meta-analysis of the epidemiological studies supports the TSD's conclusions. The epidemiology-based risk estimates are sufficiently reliable.

6. Comment summary: The issue of carcinogenicity of diesel exhaust is being assessed by three separate organizations, the California EPA, the federal EPA, and the Health Effects Institute. Since each organization draws upon the same technical literature to make its assessment, there should be no technical reason for the different organizations to draw different conclusions. The commenter encourages ARB and OEHHA to work with the other organizations on the issue of carcinogenicity of diesel exhaust to obtain consensus on common conclusions. (Letter, p. 2)

Response: OEHHA staff have worked with the other organizations towards the consensus suggested in the comment. In early 1996 OEHHA and the other organizations co-sponsored a conference on diesel exhaust cancer risk assessment epidemiology issues, and ideas from that conference are reflected in the current draft of the TSD. Cal/EPA and U.S. EPA staff have remained in contact. In particular, in its analysis of the animal bioassay data, OEHHA has included a comparative quantitative risk assessment analysis of the five rodent bioassays which closely adheres to methodology followed by the U.S. EPA. While OEHHA can not predict the future conclusions that will be drawn by U.S. EPA or the Health Effects Institute, it is anticipated based upon our similar methodologies that the range of cancer risk estimates identified in the TSD will be consistent with that being developed by the U.S. EPA.

7. Comment summary: Two main conclusions of Part B of the TSD are startling. These are: (1) OEHHA is prepared to conclude that diesel exhaust is a human carcinogen, and (2) OEHHA is proposing to recommend adoption of a cancer unit risk factor for diesel exhaust of $3xl0^{-4}$ $(\mu g/m^3)^{-1}$ derived from an epidemiology study of lung cancer incidence in railroad workers. If this factor is adopted, it would be the first time, to the commenter's knowledge, that a regulatory agency proposes a cancer unit risk factor derived from human epidemiology studies. This unit risk factor is substantially higher than that derived from lung tumor incidence observed in rats exposed by inhalation to whole diesel exhaust.

The report deals with, but does not shed any new light on the whole gamut of controversial issues at the heart of cancer risk assessment debated over the last 20 years. It does, however, raise a new issue in offering a calculation of a unit risk factor based on human epidemiology studies. The calculation of a unit risk factor for diesel exhaust based on the Garshick epidemiology data is an interesting hypothesis-generating exercise, but the exposure estimates, necessary to quantify the response, are only a plausible guess and cigarette smoking is a major confounding factor for which there was no adjustment. Consequently, the report should provide a much more comprehensive technical justification for putting forth the calculated value as the unit risk factor for diesel exhaust, as it does on page 7-21. (Comments, pp. 1-2, 4)

Response: With regard to whether diesel exhaust is a human carcinogen, the. TSD thoroughly evaluates the increased relative risks of lung cancer observed in the epidemiologic studies and their association with diesel exhaust exposure.

Quite a few unit risk values (e.g., benzene, arsenic, nickel) have been based on data from human epidemiological studies. Thus the document does not raise a new issue in this regard.

With regard to the exposure estimates in the risk assessment and to the issue of smoking as a confounder, see response to Comment 4, above. The TSD now provides a more comprehensive technical basis for the human data-based risk assessment. In addition, the document focuses on a range of unit risk values.

8. Comment summary: The main general issue raised in the document is the standard of proof necessary to reach the conclusion that diesel exhaust is a human carcinogen. Despite a rather thorough listing of the scientific unknowns, the report considers the evidence conclusive. It is very difficult to understand how the report can reach this definitive conclusion and, on the other hand, list numerous reasons why it is not possible to be definitive. It appears to the commenter that the strongest statement supported by the evidence is that the epidemiological studies suggest a possible, but very weak, association between increased lung cancer incidence and railroad occupations wherein workers were exposed to diesel exhaust. A causal link between exposure to diesel exhaust and increased incidence of lung cancer cannot be inferred because of the absence of measurements of diesel exhaust exposure in the epidemiological studies, the multiple sources of ambient airborne particulate matter, and the inability to correct the epidemiology data for the confounding effects of cigarette smoking. In any study in which the only measurable is total particles, it is impossible to attribute the observed effects (e.g. lung cancer) to one specific source of particles. (Comments, pp. 2-3)

Response: Regarding whether diesel exhaust is a human carcinogen, the TSD now includes a meta-analysis of the epidemiological literature. The TSD thoroughly evaluates the increased relative risks of lung cancer observed in the epidemiologic studies and their association with diesel exhaust exposure. Even if a study measures exposure only in terms of particle mass per volume of air, if there is only one source causing an elevated concentration of particles, it is reasonable to consider attributing observed elevated rates of adverse health effects to the emissions from that source.

9. Comment summary: Several investigators, cited in the report, have estimated unit-risk factors for diesel exhaust based on the animal studies. The report presents a similar analysis. The scientific literature is immense concerning cancer risk assessment of chemicals based on animal studies. There is a prominent faction within the toxicology community that believes that human cancer risk assessments cannot be derived from animal data. There is also an equally prominent faction that believes it is a valid means of assessing relative risks. The available evidence suggests that the animal-based risk analysis may be useful for developing hypotheses and establishing relative research priorities, but there are too many unknowns for it to be used as a regulatory tool.

In the case of animal-based risk assessments of diesel exhaust carcinogenicity, there is a problem not addressed adequately in the cancer risk assessment literature. The problem is that the rat lung tumors can be explained as a particle-only effect, i.e., the chemical composition of the particles does not matter. Tumors were observed only for the rats exposed to very high concentrations, and it has been suggested, but not proven, that very high particle concentrations in the lungs kill cells, inducing thereby cell proliferation to replace dead cells. The enhanced cell proliferation rate increases the spontaneous tumor formation frequency. It is unclear how any of the models used to calculate the dose-dependence of tumor formation take into account this mechanism. The widely used Moolgavkar, Knudsen and Venzon (MKV) model takes into account cell proliferation in the course of tumor development, but it does NOT take into account cell proliferation of normal cells as a mechanism for enhancing tumor formation.

At the few diesel-particle exposure concentrations for which rat lung tumors were observed, the tumor incidence increased nonlinearly with increasing concentration. Thus the validity of a linear extrapolation model is highly questionable.

In a sense, the risk-assessments based on the animal data are irrelevant because OEHHA developed a risk assessment based on the Garshick studies. (Comments, pp. 3-4)

Response: The use of experimental animals is and has historically been a cornerstone of toxicological research and associated regulation. For a vast number of potential carcinogens, epidemiological evidence alone is either absent or insufficient. In the case of diesel exhaust, we have both human epidemiological and animal bioassay information of suitable quality for quantitative risk estimation. Though the comment is correct that extrapolation from animal studies in general involves considerable uncertainty, there are numerous cases in consumer product testing and in environmental contaminant assessments of successful use of experimental animals. There are also cases in which animal models appear to be less sensitive to deleterious

effects than are humans. For example, the animal models (mice) for benzene-induced leukemia underestimate the actual observed rate of cancer in benzene-exposed workers. Animal studies do not, therefore, always overestimate adverse effects in humans.

As stated in Part B's Chapter.6, the mechanism of action by which diesel exhaust induces lung tumors in rats is not established; i.e., it cannot be explained as a particle-only effect. Nevertheless, a particle-only mechanism would probably include chronic inflammation and associated production of inflammatory cytokines and increased cell proliferation. As noted in a recent paper by Gaylor and Zheng (1996), even a nongenotoxic carcinogen that increases the cell proliferation rate by augmenting an endogenous mechanism is not likely to have a threshold dose. Thus a threshold model would not be adequate for a particle-only effect.

Contrary to the assertion in the comment, the MKV model can take cell proliferation of normal cells into account through the mutation rate of normal cells. Moolgavkar, Dewanji and Venzon (Risk Analysis, 8, 383-392, 1988) in their Eq. 12 show the role of that rate in the approximation used by Thorslund et al. (1987). The Moolgavkar equation in TOX_RISK (Crump et al. 1993), used in Section 7.2, is based on this approximation, assuming constant mutation rates. Thus, in a very limited way the current analysis takes any such cell turnover into account. Use of more information about time dependence of such proliferation would necessitate calculations for the more general MKV model.

The response based on animal data is clearly nonlinear. The role of the models is to use that large response so as to interpolate the risk in the range of very low exposures, where the response is small and where theoretical reasoning shows that the response should be linear.

The rat lung tumor data have not been shown to be mechanistically irrelevant to human cancer risk from diesel exhaust inhalation and, with uncertainties acknowledged, provide information useful in the characterization of the potential human cancer risk associated with diesel exhaust exposure.

10. Comment summary: The available evidence does not permit any conclusions to be reached about the risk from the organic compounds associated with diesel exhaust particles. Since the rat lung tumors can be explained as a particle-only effect (see the previous comment), nothing can be said about the carcinogenicity of the organic fraction of diesel particles. (Comments, p. 5)

Response: The TSD does not reach any quantitative risk assessment conclusions that relate only to the organic compounds associated with diesel exhaust particles. Note that as stated in Part B's Chapter 6, the mechanism of action by which diesel exhaust induces lung tumors in rats is not established; i.e., it cannot be explained as a particle-only effect. The possibility that genotoxicity due to the PAH and nitroPAH content (either particle-adsorbed or in the semivolatile phase) of diesel exhaust plays a role in the induction of lung tumors in rats at lower levels of diesel exhaust cannot be excluded. This mechanism would probably be relevant to human cancer risk, and would not be expected to have a threshold of action. Chapter 5 of the TSD describes extraction under physiological conditions of mutagens from diesel exhaust, as well as increased lymphocyte DNA adducts in humans occupationally exposed to diesel exhaust.

Comments of U. Heinrich and Donald L. Dungworth of Fraunhofer-Institut für Toxicologie und Aerosolforschung

1. Comment summary: Regarding Section 5.4 of Part B of the draft TSD: Recent work by Gallagher et al. did not reveal any significant elevation of DNA adducts in lungs of rats exposed to diesel exhaust for up to 2 years. (Comments dated September 30, 1994, p. 1)

Response: As noted in Chapter 5 of Part B, a report by Gallagher et al. (1994) indicated that no increase in total PAH-derived lung DNA adducts were observed in rats exposed to diesel exhaust for up to 2 years. However, a nuclease P1-sensitive adduct, stated by the authors to possibly result from exposure to nitro PAHs, was observed in the lungs of rats exposed to diesel exhaust but not in rats exposed to carbon black or TiO^2.-

2. Comment summary: Regarding the text on cancer studies in mice: Recent thorough studies have shown no increase in lung tumor incidence in two strains of mice. The current conclusion, therefore, is that diesel exhaust does not cause significant elevation of lung tumors in NMRI and C57BL/6N mice. Of the three animal species tested therefore (rat, mouse, hamster), the pulmonary carcinogenicity of diesel exhaust has been positive in only one - the rat. The statement about studies being positive in rats and mice in Section 6.1.1 should be changed, as should the last sentence in Section 1.3.1. (pp. 1-2)

Response: The sections of the TSD referenced in the comment have been revised to characterize the results of carcinogenicity studies of diesel exhaust in mice as mixed. The TSD has been revised to include discussions of recent mouse bioassays by Heinrich et al. (1995) and Mauderly et al. (1996). Nevertheless, the TSD does not estimate human cancer risk from mouse tumor data.

3. Comment summary: Regarding the last paragraph of Section 6.1.5: This should reflect current evidence for the induction of lung tumors in rats by diesel exhaust being mainly a non-specific particle effect. Carbon black and ultrafine titanium dioxide have similar carcinogenic potency in the rat lung as diesel exhaust. The sequence of pathologic changes with time (inflammation, hyperplasia, metaplasia and eventually some tumors) is the same whether the inhaled particles are carbon black, titanium dioxide or diesel exhaust.

The evidence is strong that particle-induced tumors in the rat are a rat-specific phenomenon. A similar effect might conceivably occur in human lungs, but comparison of effects of coal dust in rats (considerable hyperplasia, metaplasia and some tumors) with coal workers pneumoconiosis (less hyperplasia, no squamous metaplasia and no tumors) indicated this is unlikely, although coal dust consists of rather coarse particles compared to the ultrafine particles of diesel soot, carbon black, and titanium dioxide.

The toxicity of the ultrafine particles is, and their carcinogenic potential may also be, higher compared to the effect of larger particles. This was demonstrated with titanium dioxide. (p. 2)

Response: It is possible that diesel exhaust particles are capable of causing non-specific particle effects. As stated in Part B's Chapter 6, the mechanism of action by which diesel exhaust induces lung tumors in rats is not established. Nor is it established to be rat-specific. The sequence of pathologic changes mentioned in the comment includes inflammation, which is associated with production of inflammatory cytokines and, in this case, increased cell proliferation. As noted in a recent paper by Gaylor and Zheng (1996), (1) a threshold dose is questionable if a carcinogen acts via a cell receptor, (2) even a nongenotoxic carcinogen that increases the cell proliferation rate by augmenting an endogenous mechanism is not likely to have a threshold dose, and (3) dose response curves for cell proliferation and tumor incidence do not necessarily mimic each other. This casts doubt on whether, as suggested by the comment, the postulated non-specific particle-induced tumorigenesis must involve and follow a sequence of diffuse observable stages (inflammation, hyperplasia, metaplasia) prior to the appearance of distinct tumors.

As described in Chapter 4, a variety of specific adverse pulmonary effects of diesel exhaust have also been observed in several species, including human volunteers. Animal studies indicate that diesel particulates are more potent than carbon particle control exposures in induction of various pulmonary lesions (Ichinose et al., 1995; Nikula et al., 1995; Ulfvarson et al., 1995). The non-cancer effects of diesel exhaust compared with controls exposed to non-diesel particulates are of a significantly greater magnitude in guinea pigs examined using electron microscopy (Nagai et al., 1996). Diesel exhaust particles also are potent initiators of pulmonary inflammatory and localized immunological responses in humans and mice (Diaz-Sanchez et al., 1994; Fujimaki et al., 1995). The mouse cancer bioassay data are mixed, not clearly negative, so a carcinogenic response in mice from diesel exhaust is a possibility. It is apparent that diesel exhaust particles have a number of toxicological properties associated with them that cannot be ascribed merely to their particulate nature, nor to the response of a single species.

As suggested in the comment, the toxicity of ultrafine particles is, and their carcinogenic potential may also be, generally higher compared to the effect of larger particles. Coal dust does not have the same particle size distribution as diesel exhaust, nor does it have a coating of PAHs and nitro PAHs or an associated semivolatile phase containing a number of carcinogens. Diesel exhaust particles are closer in character, for example in particle size, to carbon black particles than to coal dust. A comparison of effects of carbon black and diesel exhaust for rats and for humans is presented in Appendix C of the revised TSD Part B. The different physical character of coal dust makes it of limited use in testing hypotheses about the whether the effects of diesel exhaust observed in animals can be extrapolated to humans.

4. Comment summary: Regarding text in Sections 1.5 and 7.2.2: The issue of threshold can be approached in a number of ways. From the points of view of the evidence for a non-specific particle effect in the rat (epigenetic effect) and the emergence of tumors from a background of severe hyperplasia and metaplasia, there is a high probability of a threshold effect in the rat lung. One approach to a numerical value for a threshold has been published by the World Health Organization. This is based on threshold for compromised lung clearance and gives an RfC or benchmark concentration of 2 to 3 $\mu g/m^3$. Another approach is to consider the production of pulmonary hyperplasia and metaplasia to be a necessary prerequisite for subsequent development

of tumors. This would result in a threshold value the same as calculated for non-carcinogenic effects, i.e., 5 $\mu g/m^3$. (p. 3)

Response: The proposed threshold determination suggested in the comment excludes consideration of several factors, including the mutagenic potential of diesel exhaust, and would not be appropriate for the tumor response. The analyses mentioned in the comment (W.H.O., 1996; U.S. EPA 1994) are discussed in Chapter 4 of the TSD and are applicable to the issue of a chronic non-cancer reference exposure level. Neither W.H.O. or the USEPA advocates the use of these threshold non-cancer values for use in cancer risk assessment. Both approaches mentioned by the commenter neglect to consider multiple mechanisms for toxicity and carcinogenicity by diesel particles (i.e. purely particulate effects as well as direct or indirect genotoxic mechanisms and/or immunotoxic mechanisms). Evidence, including indications of the bioavailability of known genotoxic and carcinogenic compounds on diesel particles, requires that multiple mechanisms be considered.

The findings of Gaylor and Zheng (see response to Comment 3) suggest that a non-specific particle-induced tumorigenesis need not have a threshold dose. In addition, the possibility that genotoxicity due to the PAH and nitroPAH content of diesel exhaust plays a role in the induction of lung tumors in rats at lower levels of diesel exhaust cannot be excluded. This mechanism would probably be relevant to human cancer risk, and would not be expected to have a threshold of action. Chapter 5 describes extraction under physiological conditions of mutagens from diesel exhaust, as well as increased lymphocyte DNA adducts in humans occupationally exposed to diesel exhaust. Note that the Moolgavkar model used in conjunction with the Mauderly rat data indicates that there is not a threshold apparent in the rat lung tumor data (see Table 7-4).

5. Comment summary: Regarding the rodent bioassay-based quantitative risk assessment in Section 7.2: Evidence for a rat-specific particle effect (see comment 3, above) causes considerable uncertainty about the validity of extrapolating a unit risk from rats to humans. This should be included in point 4 of Part B's Section 7.2.5. Although there are uncertainties in use of rat data, they are believed in Germany to be a better basis for calculation of unit risk than the human epidemiologic findings. Use of the rat data in Germany has given a unit cancer risk for diesel soot of 7×10^{-5}. (pp. 3-4)

Response: The TSD has been revised (Part B, Chapter 7) to acknowledge more uncertainties in extrapolating human cancer risk from rat lung tumor data. The comment does not explain why the rat data should be preferred over human data. Generally, human data are preferred by OEHHA staff because they often do not have so much of a range of extrapolation, and they do not run into difficult issues of different possible mechanisms of action among species.

6. Comment summary: At the end of point 4 of Section 7.2.5 (on page 7-10), there is the statement that the fact that background lung cancer rates are higher in humans than in rats would increase human estimates of risk based on scaling data from rats. This statement is misleading. The background lung cancer rate in the Fischer 344 rat is approximately 2.5% in males and 1.5% in females (Rittinghausen et al., Pathobiology of the Aging Rat, ILSI Press Washington DC, Vol.

1, pp. 161-172, 1992). This is considerably higher than the background rate in non-smoking humans. (p. 3)

Response: The revised TSD Part B provides numerical results of calculations that can help clarify this issue. Using the values in Table 7-1, the lifetime risk of lung cancer in the rats of the control group in the study of Mauderly et al. (1987) is, 2/230 = 0.9%. Table E-1 derives the lifetime risk of lung cancer in all Californians, including smokers, as 2.5%, which is greater than the control risk for these rats. Table 7-11 calculates that the lifetime risk of lung cancer in a population of non-smokers is 0.34%, which is less than the control risk for these rats. Two ways to adjust for the difference between the control risk for the rats and the population risk for humans are readily apparent. One way is to adjust the rat risk to humans by multiplying by the ratio of human to rat risk, adjusting up for the California population, as in the risk assessment, and down for nonsmokers. The other way, discussed in Section 7.5 of the revised TSD, is to convert the absolute rat risk to an absolute human risk for non-smokers and then adjust that risk up by the ratio of the risk in the California population to the risk in the non-smoker population. A discussion of this is now in the revised TSD, Section 7.5.3.

Comments of The Gillig Corporation

1. Comment summary: The commenter questions the scientific relevance of much of the research discussed in the TSD to classifying diesel exhaust as a toxic and to future rule making. The commenter's primary concern is the age of the data cited in the TSD. Diesel emission development has accelerated tremendously in recent years, yet data cited is all from 1990 and prior years. There have been two emission standard changes and one fuel formulation change since then. Indeed, the character of diesel exhaust has changed significantly in the past 4 years.

The TSD frequently cites 1989 Volkswagen diesel exhaust studies as if relevant to California where the primary contribution is from heavy duty vehicles. Volkswagen stopped importation of diesel vehicles to the United States because they could not meet our emission standards. The commenter feels that contemporary studies from U.S. technology leaders are more appropriate in contributing to future policy. Fuel analysis in the TSD is based on 1990 fuels and earlier. Your agency is also planning on further changes to fuel formulation. The commenter feels it is reasonable to base future toxic policy, with future regulatory impact, on current fuels and technology and projections, rather than on the past.

Many of the medical studies cited in Part B are out of date. The cited studies of diesel exposure date back to 1978 - years before most diesel emission standards were in force. The nature, composition, and concentration of diesel exhaust has changed markedly.

Throughout the draft, the dates of cited reports are misleading as to their content and timeliness. For example, a 1987 report on diesel exhaust in an animal test chamber (by Mauderly et al.) uses a 1980 Oldsmobile engine as an exhaust source. This same report is cited throughout the document. (Letter from Charles E. Koske, V.P. of Engineering, dated September 15, 1994, pp. 1-2)

Response: It is likely that the composition of diesel exhaust does vary somewhat with engine (source) type, year and fuel formulation. Whether these variations importantly impact the risks associated with diesel exhaust cannot be assessed without quantitative speciation of the components of the exhaust at issue and an index of the toxicological concern associated with each of the measured components. Because this information is not available, we have not been able to take into account differences among types of diesel engines, model years, or fuels. The Air Resources Board is sponsoring work to speciate the components of current diesel exhaust.

Part B of the TSD discusses genotoxicity studies which indicate that changes in diesel fuel composition have not been demonstrated to eliminate exhaust genotoxicity, and that changes in engine type and year have a relatively small effect on the magnitude of diesel exhaust genotoxicity (see Chapter 5). The TSD also discusses studies on rats which largely found similar doses of diesel exhaust to have about the same carcinogenic effects even though several different engine types and fuels were used to generate diesel exhaust (see Chapter 6).

Changes in engine design could reduce or heighten the risk associated with a given mass of diesel exhaust particles (e.g., by producing particles of different size).

The document does point out the model year of the engine in the Mauderly et al. study (in Chapter 6).

2. Comment summary: The commenter's review of carcinogenicity studies (including Pepelko and Peirano 1983) showed them to be dated enough to question the fuels and exhaust characteristics that they used. Even studies as late as Takemoto et al. (1986) used uncontrolled engines as the exhaust source. The scientists involved must believe that all diesel exhaust is the same, but we know from ARB certifications that that is incorrect. (P. 2)

Response: The time required for design and conduct of carcinogenicity studies with laboratory animals is often more than 5 years and sometimes up to 10 years. The long latency of cancer suggests that epidemiologic data relevant to the most recent exposures will not be available for many years. Therefore it is unlikely that any currently available study results could be based on exposures to the most recent diesel technology.

3. Comment summary: Many researchers draw the conclusion that relative risk is linear to dose. Nowhere in the TSD are these linear models applied to the improvements in diesel exhaust emissions that EPA and ARB standards have forced. We are left with relatively out of date studies such as Garshick et al. (1988) on railroad workers in 1959 through 1980 as establishing California's future policies that will impact trade and employment in the entire state -- while not providing a real health benefit. (p. 2)

Response: Part B's (linear model-derived) unit risk estimates are applied to exposure estimates provided by ARB. The exposure estimates are current. They reflect "improvements" in emissions that have resulted from government standards. The TSD is intended to give an assessment of risks at current levels of exposure, and a dose-response assessment that can be applied to current or future exposures. If diesel exhaust is listed by regulation as a toxic air contaminant, ARB will

take projected (future) exposure levels into account when considering further measures regarding diesel exhaust.

4. Comment summary: The commenter questions the extrapolation of aged health studies on coal miners, railroad workers and stevedores, to the general public whose primary exposure is through vehicles with very improved emission characteristics and very different environmental conditions. The commenter feels that basic studies that will have significant future impacts should be based on current and pending emission standards. We also feel since the ARB issues emission regulations on these engines and fuels, the health portion of the TSD should reference the ARB regulations. Utilizing old, uncontrolled emissions as a basis for health studies that will drive future policy does a disservice to California's economy, trade and employment. (pp. 2-3)

Response: The TSD is intended to give an assessment of risks at current levels of exposure, and a dose-response assessment that can be applied to current or future exposures. If diesel exhaust is listed by regulation as a toxic air contaminant, ARB will take projected (future) exposure levels into account when considering further measures regarding diesel exhaust.

Comments of Industrial Compliance
(on behalf of Southern Pacific Transportation Company)

1. Comment summary: In general, Cal/EPA has provided an extensive and well-documented discussion of health and risk assessment issues related to diesel exhaust. However, considerable uncertainty remains regarding the TSD (Part B)'s primary conclusions that (1) there is sufficient evidence from human epidemiologic studies that occupational exposure to diesel exhaust contributes to lung cancer, and (2) there is no threshold effect for carcinogenicity of diesel exhaust. These conclusions have not been adequately established and should not be used in the evaluation of diesel exhaust as a "toxic air contaminant." (Comments dated October 13, 1994, pp. 1-1 - 1-2)

Response: (1) Regarding whether diesel exhaust is a human carcinogen, the TSD thoroughly evaluates the increased relative risks of lung cancer observed in the epidemiologic studies and their association with diesel exhaust exposure. (2) The TSD does not conclude that there is no threshold for carcinogenicity of diesel exhaust. It concludes that the available data do not establish the existence of a threshold.

2. Comment summary: Because of significant limitations and methodological flaws, epidemiologic studies are unable to support a causal relationship between diesel exhaust and either non-cancer respiratory health effects or lung cancer at occupational exposure levels. This suggests that occupational diesel exhaust exposure levels are below the threshold for human health effects. This indicates that the risk of health effects to the general public is negligible given the much lower exposure potential. (p. 1-1)

Response: The TSD now includes a meta-analysis of the epidemiologic studies. The meta-analysis evaluates the consistency of the relationship between occupational exposure to diesel

exhaust and lung cancer. The evaluation of the potential for non-cancer effects is based mainly on studies of laboratory animals.

3. Comment summary: Occupational exposure levels to diesel exhaust have not been shown to be associated with genotoxicity. Positive genotoxicity results in various in vitro and in vivo bioassays have generally been obtained under extraordinary conditions, with high concentrations of extracts obtained by treating diesel exhaust particulates with strong organic solvents. This approach presents the biological system with a large quantity of test material in a very short period of time and bypasses many of the protective mechanisms encountered when diesel exhaust is inhaled. Thus, the relevance of these types of tests for evaluation of diesel exhaust exposure in man is questionable.

Inhalation studies in which animals or humans were directly exposed to diesel exhaust are more representative of actual exposure conditions. Most studies conducted in this manner have been negative. Two positive studies of direct diesel exhaust exposure were identified, however, genetic activity was 3 reported only at air concentrations greater than 6 mg/m^3. Exposures of this magnitude are extremely unlikely to occur in occupational settings or over an extended time period. Studies of humans confirm that occupationally-related exposure to diesel exhaust is not associated with evidence of genotoxicity. (pp. 1-1, 1-3, 4-1 - 4-4)

Response: The Part B document has been revised to include discussion of 1) studies which indicate that extraction with a phospholipid emulsion resembling a major component of lung surfactant showed substantial mutagenic activity, sometimes greater than that observed after extraction with organic solvents (Chapter 5); 2) data indicating that both animal and human occupational exposure to diesel exhaust has been shown to result in the production of urinary metabolites of PAHs and nitroPAHs, indicating bioavailability of those compounds (Chapter 3); 3) data describing formation of a nuclease P1-sensitive adduct in the lungs of rats exposed to diesel exhaust which is not found in rats exposed to carbon black or TiO^2; 4) studies which show that formation of human lymphocyte DNA adducts is associated with occupational exposure to diesel exhaust (Chapter 5). This information is relevant to diesel exhaust exposure of humans; it suggests that the induction of lung cancer in humans associated with diesel exhaust exposure may occur through a non-threshold genotoxic mechanism.

Quantitative exposure level determinations were not done in the human occupational adduct studies. OEHHA staff were unable to validate the statement in the comment that genetic activity was reported only at air concentrations greater than 6 mg/m^3.

4. Comment summary: The animal data are consistent with thresholds for pulmonary function and carcinogenesis, most likely related to the point at which the lung's natural defenses become overwhelmed by the amount of particulate matter being inhaled. Extrapolation of this data to humans indicates animal dose levels associated with carcinogenicity are significantly higher than those likely to be encountered by human populations.

Exceedingly high concentrations can cause respiratory problems through a mechanism in which the lung's natural defenses are overwhelmed by the sheer amount of particulate matter. Clearly,

this is a phenomenon which would not be specific to diesel exhaust particulates and, in fact, has been shown to occur with other particulates such as carbon black and titanium dioxide. Tests such as these do not provide useful information for estimating health effects from human exposure levels.

As the TSD suggests, particle overload and the resulting inflammation and cell turnover in the lung are likely explanations for the carcinogenic activity of diesel exhaust in rats. Rats appear to be more susceptible to this effect than other species (i.e., monkeys) and may not be an appropriate model for estimating carcinogenic risk from diesel exhaust inhalation. As with non-carcinogenic effects, carcinogenic effects are seen in animals at air concentrations and durations which are unlikely to be encountered through occupational exposure. Thus, the use of unrealistic exposure conditions, combined with the use of an animal species which appears to be uniquely at risk from particulate inhalation, makes the animal carcinogenicity findings of questionable relevance to human risks from diesel exhaust exposure. (pp. 1-1 - 1-4)

Response: Animal data give only a single study from which to draw conclusions about pulmonary function. In the Lewis et al. (1986) study, monkeys were exposed to 0 or 2 mg/m^3 diesel exhaust. Deficits in pulmonary function were found in the monkeys exposed to diesel exhaust. As the study included only one diesel concentration, no NOAEL was observed. It is therefore not possible to determine a threshold for pulmonary function effects from this study. OEHHA staff do not dispute the possible presence of a threshold for the onset of adverse pulmonary function effects from diesel exposure. However, the case of a threshold for diesel exhaust-induced carcinogenicity is far from clear, and requires consideration of many factors (see below). The meta-analysis now included in Part B of this TSD is an indication that such a threshold, if it existed, would lie below levels of diesel exhaust to which humans have been exposed.

The mechanism of action by which diesel exhaust induces lung tumors in rats is not established. One proposed mechanism is that exposure to diesel exhaust particulate matter at high concentrations exceeds pulmonary clearance capabilities and causes chronic inflammation. This inflammation leads to macrophage and/or neutrophil-induced oxidative DNA damage resulting in mutations which are instrumental in the induction of lung tumors, and also leads to cell proliferation which may be mechanistically important to the promotion of the rat lung tumors. This mechanism may have an exposure threshold of action. However, the possibility that genotoxicity due to the PAH and nitroPAH content of diesel exhaust plays a role in the induction of lung tumors in rats at lower levels of diesel exhaust cannot be excluded. This mechanism would probably be relevant to human cancer risk, and would not be expected to have a threshold of action. (Chapter 5 of Part B describes the extraction under physiological conditions of mutagens from diesel exhaust, as well as increased lymphocyte DNA adducts in humans occupationally exposed to diesel exhaust.) In addition, the proposed overload mechanism includes chronic inflammation and associated production of inflammatory cytokines and increased cell proliferation. As noted in a recent paper by Gaylor and Zheng (1996), (1) a threshold dose is questionable if a carcinogen acts via a cell receptor, (2) even a nongenotoxic carcinogen that increases the cell proliferation rate by augmenting an endogenous mechanism is not likely to have a threshold dose, and (3) dose response curves for cell proliferation and tumor

incidence do not necessarily mimic each other. The rat lung tumor data are not irrelevant to human cancer risk from diesel exhaust.

Several animal studies described in Chapter 4 of the TSD show that the noncancer effects from exposure to diesel exhaust are more severe than those seen in concurrent controls exposed to other particulates. It does not appear, therefore, that all particulate types behave similarly regarding severity of effect.

5. Comment summary: The TSD's conclusion of carcinogenicity in humans is based on studies with significant weaknesses, The most significant weakness of the studies is the complete lack of exposure data. None of the studies provides a reliable quantification of exposure to diesel exhaust or other substances (i.e., asbestos). In many of the studies, it is questionable whether exposures above background occurred in members of the study populations.

The second major weakness is the lack of data regarding smoking. Over half of the cited studies did not perform even a cursory examination of smoking. Smoking histories in the other studies were poorly detailed or had large amounts of missing data. Of the studies which did examine smoking, well over 90% of the lung cancer cases had a positive smoking history. None of the cited studies has sufficiently accounted for the confounding effects of smoking.

The third major weakness is that the risk levels are almost all below 2.0. Many are not even statistically significant. The significance of risks of this magnitude is highly questionable since it is nearly impossible to control for all identified and unidentified confounders, the most obvious of which is smoking.

Other weaknesses are also associated with the studies. It is inappropriate and misleading for Cal/EPA to conclude that there is "a considerable degree of consistency in regard to a finding of elevated lung cancer rates in workers believed to have been exposed to diesel exhaust."

A recently published study of Finnish locomotive drivers provides evidence which is completely contradictory to the conclusions made in the U.S. railroad studies. The authors of this study found no evidence of an increased risk of lung cancer among Finnish drivers. It is important that the prevalence of smoking among the Finnish drivers is significantly lower than that in the U.S. studies. (pp. 1-4 - 1-5)

Response: Regarding whether diesel exhaust is a human carcinogen, the TSD thoroughly evaluates the increased relative risks of lung cancer observed in the epidemiologic studies and their association with diesel exhaust exposure. The TSD now includes a meta-analysis of the epidemiologic studies which quantitatively evaluates the overall significance of a group of studies without direct measurement of concentration of diesel exhaust. The meta-analysis also provides a strong indication that confounding factors such as smoking are not responsible for the excess carcinogenicity observed in diesel exhaust-exposed occupational groups. Further, the meta-analysis increases confidence in the positive findings of studies with relative risks below 2.0.

The measurements of respirable particles in the Woskie et al. (1987a,b) studies directly apply to the two railroad worker studies by Garshick et al. (1987a, 1988). Garshick et al. (1987b) address the issue of exposure to asbestos among railroad workers. In the bulk of the epidemiologic studies, exposure to diesel exhaust can be questioned, but the most reasonable assumption is that it occurred.

The comment does not offer details of how the smoking histories that were obtained in the studies "were poorly detailed or had large amounts of missing data."

The statement regarding "a considerable degree of consistency" in the worker studies has been modified somewhat. Chapters 1 and 6 of Part B now note that there is a considerable degree of consistency in finding elevated, although not always statistically significant, lung cancer risks in workers potentially exposed to diesel exhaust within several industries.

The study of Finnish locomotive drivers (Nokso-Koivisto and Pukkala, 1994) did not come to our attention in time to be included in the 1994 draft, but a review is in the current revision of Part B, Section 6.2.1.4. The chief result of the study is a standardized incidence ratio (SIR) of 0.86, which is below the SIR of 0.95 for all cancer among the drivers. These SIRs represent incidence rates below the expectations based on national values. The diesel exposure of this cohort might not be sufficient to detect an effect, as discussed in the revised TSD. The observation that Finnish locomotive drivers have a significantly lower prevalence of smoking than do U.S. drivers does not provide a comparison that is directly applicable to understanding the differing relative incidences of lung cancer between those two groups. Establishing a contradiction between the results for these two groups would require further information, such as age dependence of smoking rates in the exposed and the reference population, evaluation of the follow-up in the drivers and the actual age-dependent exposures of the workers. An explanation of the standardized incidence ratio for lung cancer being less than that for all cancer would also be required. The TSD's meta-analysis (Part B, Appendix D) finds that this study is anomalous relative to other railroad studies.

6. Comment summary: An important consideration in evaluating lung cancer in animals from diesel exhaust exposure is the relationship between exposure levels, lung clearance, and the occurrence of tumors. The data cited in the TSD indicate an apparent threshold for impairment of lung clearance in F-344 rats chronically exposed to diesel exhaust. Exposures above this level are required to increase tumor incidence in exposed animals. Clearly, assessment of the risks from low-level human exposure to diesel exhaust should account for threshold effects.

Cal/EPA has estimated cancer risks to humans from inhalation of diesel exhaust using the animal study of Mauderly et al. (1987). The assumptions and methods employed by Cal/EPA in their estimates can be shown to overestimate risk by several orders of magnitude. Areas in which the assumptions and quantitative procedures used by Cal/EPA exaggerated the animal-based risk projections include: use of all lung tumors instead of malignant tumors; forcing the dose threshold to equal zero; inappropriate time in time-to-response model prediction of human risks; assumptions regarding time-to-response model selection and parameterization; methodology

used to calculate upper bounds; no weight-of-evidence evaluation of animal studies; and, imprecise human exposure assumptions.

Of particular importance is the indication of a human dose threshold well above levels likely to be encountered in occupationally-related diesel exhaust exposures. (pp. 1-6)

Response: The mechanism of action by which diesel exhaust induces lung tumors in rats is not established. One proposed mechanism is that exposure to diesel exhaust particulate matter at high concentrations exceeds pulmonary clearance capabilities and causes chronic inflammation. This inflammation leads to macrophage and/or neutrophil-induced oxidative DNA damage resulting in mutations which are instrumental in the induction of lung tumors, and also leads to cell proliferation which may be mechanistically important to the promotion of the rat lung tumors. This mechanism may have an exposure threshold of action. However, the possibility that genotoxicity due to the PAH and nitroPAH content of diesel exhaust plays a role in the induction of lung tumors in rats at lower levels of diesel exhaust cannot be excluded. This mechanism would probably be relevant to human cancer risk, and would not be expected to have a threshold of action. (Chapter 5 of Part B describes the extraction under physiological conditions of mutagens from diesel exhaust, as well as increased lymphocyte DNA adducts in humans occupationally exposed to diesel exhaust.) In addition, the proposed overload mechanism includes chronic inflammation and associated production of inflammatory cytokines and increased cell proliferation. As noted in a recent paper by Gaylor and Zheng (1996), (1) a threshold dose is questionable if a carcinogen acts via a cell receptor, (2) even a nongenotoxic carcinogen that increases the cell proliferation rate by augmenting an endogenous mechanism is not likely to have a threshold dose, and (3) dose response curves for cell proliferation and tumor incidence do not necessarily mimic each other. The rat lung tumor data are not irrelevant to human cancer risk from diesel exhaust.

The cancer risks estimated from the Mauderly study are approximately one order of magnitude less than risks estimated from the human epidemiological data (see Chapter 7). In response to the concerns about use of all tumors, squamous cysts have been removed from the analyses in the TSD's risk assessment. Inclusion of benign precursors of malignant tumors in modeling human cancer risk from animal tumor data, however, is generally considered to be appropriate. The squamous cysts are no longer in the analyses because it is not clear if they are precursors of malignant tumors. The analyses include the use of the Moolgavkar model, which does not force the threshold to equal zero.

All animal cancer studies with diesel exhaust were examined. Section 7.2.4 of Part B discusses why the Mauderly et al. (1987) study was selected for risk assessment, although it may not give the highest potency estimates. Its selection due to superior reporting and study design may be viewed as involving an implicit weight-of-evidence analysis of the animal studies.

As described in Chapter 1, there is no clear indication of a threshold for carcinogenesis.

For more detail on animal data-based risk assessment issues, see responses to Comments 29-35, below.

7. Comment summary: Each of the three railroad studies cited by Cal/EPA as the best evidence of an association between diesel exhaust exposure and lung cancer has significant weaknesses.

The Garshick (1988) study that is used in the TSD as the basis for establishing human risk estimates has highly significant limitations which make its credibility and elevation to such a level of importance questionable. The authors of the study did not examine smoking histories among the study population. Although Cal/EPA has cited this study as evidence of a dose-response relationship, when the authors of the study eliminated the highest-exposed workers (shopworkers) from their analyses because of potential confounding from asbestos exposure, they found the relative risks actually increased slightly. Elimination of the shopworkers should have resulted in a decreased relative risk if a dose-response relationship was present. it should also be noted that the relative risks for the potentially highest exposed group also had the widest confidence interval. The differences in relative risk between the different exposure groups were all less 1.0. Thus, it is questionable whether a significant difference between any of the groups actually exists.

Considering the readily apparent weaknesses and inconsistencies, it is surprising that Cal/EPA has based its entire human risk assessment on this study. Because the study lacks information regarding exposures (to diesel exhaust, cigarette smoke, asbestos, and other potentially relevant substances), it is not an appropriate study on which to base risk calculations. Thus, the various assumptions used by Cal/EPA in establishing a cancer slope factor from this study are not valid. (pp. 1-6 - 1-7)

Response: Each of the three railroad studies referred to in the comment -- Howe et al. (1983), and Garshick et al. (1987a and 1988) -- has significant uncertainties, which the comment characterizes as weaknesses. Specific points are discussed in the following paragraphs and in response to Comment 25.

The TSD's human data-based dose-response assessment is no longer based entirely on the Garshick et al. (1988) cohort study. The revised TSD has added an exposure-response relationship for the Garshick et al. (1987a) case-control study to the quantitative risk assessment. This study does have some information on smoking, but it shares with the Garshick et al. (1988) cohort study the uncertainty about the exposure history of the railroad workers.

Notwithstanding the lack of direct measurement of smoking in the Garshick et al. (1988) cohort study, investigators (Cohen and Higgins, 1995) have stated that the elevated relative risk found in this study could not be explained by cigarette smoking. The argument refers to data from the Garshick et al. (1987) case-control study as evidence of lack of confounding due to smoking in the cohort study of the same workplace. The case-control study obtained smoking habit data from some next of kin by questionnaire.

The analysis of the Garshick et al. cohort study in the revised TSD has been modified to exclude shopworkers. That job did have some very highly exposed workers and also some workers with virtually no exposure, but the actual proportion of exposed-to-unexposed is not known. Hence the exclusion. The revised TSD shows that, due to their very heterogeneous exposure, the overall

risk of shopworkers is most likely to be about the same as for train workers. On this basis, the very small reduction of risk with shop workers removed, as reported in Garshick et al. (1988), is well within the random variation of the data. It is correct that the apparently most highly exposed group had the widest confidence interval. This reflects the choice of category boundaries that resulted in less cancer deaths in that group. Although the maximum likelihood estimates of relative risk are all below 2, the three highest exposed groups were all just significantly above 1. Moreover, the trend is statistically significant. In sum, the cancer slope factors calculated from Garshick et al. (1988) are based on valid assumptions and are themselves valid representations of overall slope.

Because of questions about these results, the revised TSD (Appendix E) includes an analysis starting with the individual data and showing substantial statistical significance. Also included (Appendix D) is a meta-analysis, positive with 31 studies. The meta-analysis should substantially address the concerns, raised by this and other commenters, regarding confounding.

8. Comment summary: Appendix B of Part B discusses what Chapter 4 describes as "an extensive series of epidemiologic studies" that "has provided evidence that ambient particulate matter may be associated with serious health effects, including death." The relevance of these studies to an evaluation of the health effects of diesel exhaust is questionable since the studies did not specifically examine diesel exhaust; in many of the studies the source of particulate matter is known to be something other than diesel exhaust (i.e., burning wood, coal, factories, etc.). These references are misleading and should not be used to support conclusions regarding diesel exhaust. (pp. 1-2, 3-1)

Response: The purpose of the discussion of the epidemiological studies is to illustrate the types of health impacts that occur following chronic exposure to airborne particulates, including diesel exhaust. The document does not use the studies for quantitative risk assessment for diesel exhaust. Several recent clinical studies specifically examining the effects of instilled diesel particles on immunologic and allergic responses in human volunteers are now described in Chapter 4 and can be used to support the conclusions (regarding particles, not diesel exhaust) drawn from the epidemiological studies mentioned. The health assessment of diesel exhaust would be incomplete without some discussion of particles. Diesel exhaust does contribute to environmental particle load and many of the issues surrounding diesel exhaust relate to the effects of its particles.

9. Comment summary: Near the bottom of page 4-3, the TSD cites four epidemiologic studies. Each has significant weaknesses in terms of exposure data, possible confounding by smoking, small study populations, and inconsistent study results. For the most part, the weaknesses of the studies have been recognized by Cal/EPA. Therefore, the TSD's conclusion that the studies "suggest together that exposure to diesel exhaust may be related to respiratory symptoms" is surprising. The TSD should state that these studies provide little support for non-cancerous respiratory effects of diesel exhaust at occupational exposure levels. (pp. 1-2 - 1-3)

Response: One of the studies (Reger et al. 1982) is no longer cited. As now restated in the revised TSD, the remaining studies mentioned in the comment, though not entirely consistent, do

suggest that respiratory symptoms and/or pulmonary function may be due to exposure to diesel exhaust. Later in the same paragraph, the TSD states that seven studies did not find respiratory symptoms or pulmonary function changes in the subjects examined. The TSD acknowledges weaknesses present in the studies.

Diesel exhaust contributes to ambient particulate matter, which is a serious public health problem. Appendix B of this TSD provides a summary of this problem.

10. Comment summary: The TSD's discussion of non-carcinogenic health effects of diesel exhaust exposure in human epidemiologic studies is somewhat misleading. The document correctly notes that all of the studies had limitations such as small numbers of subjects and inadequate exposure characterization. However, the document's comments regarding each cited study do not always give an accurate representation of the article's contents.. For example, the discussion of Battigelli et al. (1964) omits perhaps the most important finding of this study, which is the effect of smoking on respiratory symptoms and function.

Part B fails to note that factors such as recall bias or different work conditions among underground miners unrelated to diesel exhaust (i.e., increased dust, temperature, humidity etc.) may explain the findings by Jorgensen and Svensson (1970) of increased bronchitic symptoms.

Chapter 4's statements that important effects or relationships could have been "obscured" in certain studies (Ames et al. (1982) and Attfield et al. (1982)) lack objectivity and assume that there must be some effect.

Cal/EPA has failed to note that Reger et al. (1982) concluded that differences in selected symptoms and pulmonary function performance between matched pairs relative to an index of exposure did not show trends consistent with an effect due to diesel emissions.

Cal/EPA notes that Gamble et al. (1983) found an increased prevalence of phlegm associated with exposure to diesel exhaust. However, given the study's extremely low risk ratios, incomplete exposure characterization, incomplete controlling for smoking (i.e., classified only as current, ex- or non-smoker), and inconsistencies in symptom findings (i.e. cough or dyspnea, not associated), one cannot conclude any kind of causal relationship between the findings and diesel exhaust exposure.

The TSD fails to note that Robertson et al. (1984) concluded that "with the current levels of these gases, any long term effects on respiratory health are so small as to be undetectable in the presence of smoking and dust exposure."

The TSD fails to note that Ulfvarson et al. (1987) could not find any dose-related correlation between nitric oxide, nitrogen dioxide, formaldehyde, or carbon monoxide and pulmonary function. Also, there was no control group used to compare the pulmonary function findings, and the number of individuals who experienced a decline over the workshift, and the number of these individuals who were smokers is not given. It should be noted that the method of recruitment of

study participants and hence their motivation for participation in the studies by Ulfvarson is not clear.

Other observations can be made with regard to other studies. In addition, the three studies by Ulfvarson et al. have serious methodological flaws and cannot support a causal association between pulmonary function measurement decreases and diesel exhaust exposure at the levels cited. The most logical conclusions from the studies reviewed by Cal/EPA are that the results have been highly inconsistent, dose-response relationships have not been established, the studies are severely limited by confounding from smoking or other exposures unrelated to diesel exhaust, and recall, selection, and volunteer biases make any meaningful interpretation impossible. Positive findings in these studies have been extremely small in magnitude and could be easily explained by one or more of the above factors. Thus, these epidemiologic studies provide little support for non-cancerous respiratory effects of diesel exhaust at occupational exposure levels. This fact should be clearly stated. (pp. 1-2 - 1-3, 3-1 - 3-3)

Response: The TSD states that Battigelli et al; (1964) found no significant effects on health attributable to diesel exposure of workers. The study's findings regarding smoking, while important, as suggested in the comment, are not directly relevant to diesel exhaust, the subject of the TSD.

The study by Jorgenson and Svensson (1970) found a significant increase in bronchitic symptoms of tightness of the chest and cough in 60 underground miners compared with symptoms from 55 above-ground workers, although spirometry results were negative. The dust conditions of the mine were reportedly "well under control", and were generally between 300 and 600 particles/cubic centimeter, according to the authors on page 353 of the report. Data on temperature and humidity conditions were not presented in the article. There is therefore no firm basis for presenting these conditions as confounding variables accounting for the observed effects. Recall bias would be more likely if the exposure occurred much before the measured responses, thus making a precise recollection of exposure conditions more difficult. In the Jorgenson and Svensson study, measurements were taken immediately after the end of the workshift. In addition, recall bias, if present, could just as easily influence the results toward lesser severity. There is no reason to suppose that recall bias occurred or that it only influenced the results in one particular direction.

The study by Ames et al. (1982) included an exposed group of 60 miners. With such a small sample size, an important effect might have been obscured, and this possibility is mentioned in the TSD. Additionally, the age of the controls was 15.1 years greater than the exposed group, on average. A large effect would have been required in order for a statistically significant difference to become apparent between the two groups.

Similarly, Attfield et al. (1982) found that symptom prevalences in potash miners were elevated compared with a non-dust exposed group of workers, which the investigators indicated "...may have caused difficulty in the detection of dose-response relationships..." of diesel exhaust with respiratory symptoms. Type-II errors are a common concern in epidemiology, particularly when confounding variables related to potential adverse effects are known to exist. The major

limitations of the Ames et al. (1982) and Attfield et al. (1982) studies probably biased the results in the "no-effect" direction. The TSD, therefore, uses caution in interpretation of statistically negative results, which is different from assuming the presence of an effect.

The study by Reger et al. (1982) found significantly elevated incidence of cough and phlegm in diesel-exposed miners, but the decreased pulmonary-function test results were not significantly different from the matched control miners. Diesel-exposed workers had less dyspnea compared with the control miners. The authors state in their abstract: "A prudent public health stance dictates reservation of judgement pending prospective examinations and detailed environmental surveys". In other words, the authors were unable to draw definitive conclusions about the results in their study. The TSD's description of Reger et al. (1982) has been expanded to clarify the conclusions reached in the report.

The TSD accurately describes both the positive and negative findings of the Gamble et al. (1983) study. The document does not claim that the studies indicate causality, but rather that the studies contain results that are consistent with those of other studies. In separate analyses of the same individuals, Gamble and Jones (1983a, 1983b) associated the increased phlegm production specifically with diesel exhaust. They (1983a) also reported a significant decrease of vital capacity with exposure to diesel exhaust, and their data suggest a trend of increasing dyspnea with diesel exhaust. Increased phlegm was associated with exposure, however, as noted in the comment. The TSD reports this effect but does not claim that the data establish causality by diesel exhaust.

Robertson et al. (1984) did find that effects at the NOx concentrations studied were insignificant compared to the influence of dust (particulates) and smoking. The TSD's summary of this study (in Part B, Chapter 4) notes that no significant differences between controls and NOx-exposed individuals were observed for respiratory symptoms or FEV1. The suggested direct quote from the study report would not add useful scientific information to the TSD.

The lack of correlation between individual gases and pulmonary function is now mentioned in the TSD's discussion of Ulfvarson et al. (1987). The workers in this study were tested for changes in pulmonary function over a workshift. The fact that a control group of workers was not also tested is not necessarily a critical component in evaluating the results since the workers were tested using before-shift values as their own "control" levels. The pulmonary function results were presented as group means, therefore the number of individuals experiencing a decline was not given. The number of individuals experiencing a decline that were also smokers is not given in the Ulfvarson et al. (1987) paper. This point has been added to the TSD in the description of Ulfvarson et al. (1987). The method of recruitment of the subjects was not explicitly stated in the report, as pointed out by the comment. This point is now mentioned in the TSD.

The more recent studies by Ulfvarson have limitations common to epidemiology studies, and contain potentially confounding variables that could influence the results in either direction. The TSD concludes the section on human non-cancer epidemiology studies (Part B, Section 4.1) with statements acknowledging the presence of limitations and possible confounding variables.

To these statements have been added mention of some of the potential variables mentioned in the comment. However, despite their limitations, nearly all of the studies indicate some degree of respiratory effects in humans from exposure to diesel exhaust. Though each individual study may not be definitive in showing a causal relationship, as a whole the effects are consistent and therefore highly suggestive of causality. The more recent studies in human volunteers showing increased inflammatory and allergic responses following brief exposures are consistent with this conclusion. It would be incorrect to state that epidemiologic studies provide little support for non-cancerous respiratory effects of diesel exhaust at occupational exposure levels. I

11. Comment summary: Together with the IRIS information on diesel exhaust (Appendix A of Part B), the animal health effects section of the TSD provides an adequate review of the animal studies of the noncarcinogenic effects of diesel exhaust.

In addition, it is worthwhile to note that in nearly all the animal inhalation studies that were reviewed, diesel exhaust exposure is expressed on the basis of the concentration of diesel particulate in air. While there is general scientific consensus that the noncarcinogenic pulmonary effects of diesel exhaust are primarily due to the particulate component of the exhaust, the role of inhaled diesel exhaust particles in inducing non-respiratory toxicity is far from clear owing to varying atmospheric fate and transport characteristics of the particulate, gas, and volatile hydrocarbon constituents of diesel exhaust, it is not known the degree to which human environmental "diesel exhaust" exposure will mimic the diesel exhaust composition of the inhalation test chambers used in animal studies. Thus, for the apparent toxic effects that have not been confidently associated with the particulate phase of diesel exhaust, extrapolation from the results of animal diesel exhaust studies to environmental human exposures should be performed with great caution. (pp. 1-3, 3-3 - 3-4)

Response: In response to this comment, it is important to note that the TSD does not engage in quantitative extrapolation of non-cancer, non-respiratory, health risks from animal studies to humans. (The commenter does not dispute the propriety of extrapolating respiratory effects.) It is also important to note that although the TSD uses particulate mass as the measure of exposure, this is not meant to imply that the observed adverse health effects are necessarily caused by the particulate fraction of the exhaust. As is made clear in the document, this measure is a dose surrogate for exposure to all components of diesel exhaust.

OEHHA staff share the commenter's concerns regarding the varying composition of diesel exhaust. Since inhalation studies discussed in detail in the TSD indicate that exposure to diesel exhaust particles results in different manifestations and severity of toxicity than a number of different non-diesel particles (see Lewis et al., 1986; Nikula et al., 1995; Ichinose et al. 1995 for 3 examples in several species), it is not clear that all adverse effects from diesel exhaust exposure are due purely to non-specific particle effects. Whether the variations in its composition importantly impact the risks associated with diesel exhaust cannot be assessed without quantitative speciation of the components of the exhaust at issue and an index of the toxicological concern associated with each of the measured components. Such information is currently not available.

12. Comment summary: The TSD fails to note that Pepelko and Peraino (1983) found that diesel exhaust treatment failed to significantly increase mortality associated with Salmonella typhimurium or the influenza virus A/PR8-34 in female CR/CD-l mice. (p. 3-4)

Response: Table 4.2, page 4-13 described the study by Pepelko and Peirano (1983) and clearly indicated that of the three pathogens tested, "only Streptococcus pyogenes infectivity was enhanced".

13. Comment summary: The discussion of the Chen (1986) study is very confusing and implies that diesel exhaust particles are more potent inducers of lung aryl hydrocarbon hydroxylase (AHH) activity than benzo[a]pyrene. The Chen (1986) study was not designed to compare the relative potency of PAHs present in diesel exhaust with benzo[a]pyrene. Further, the experimental results do not provide reasonable quantitative evidence for the conclusion that PAHs in diesel exhaust particles are more potent than benzo[a]pyrene. Secondly, this commenter questions the 1/400 to 1/2000 range quoted for the fraction of the total mass of particulate made up by PAH. The quoted IARC monograph suggests that PAHs account for at least 9% of the particulate phase of light duty diesel exhaust. In addition, the TSD provides no perspective as to the toxicological importance of AHH induction. Enzyme induction is not considered to be an adverse health effect and should be distinguished as such in the discussion. (pp. 3-4 - 3-5)

Response: The TSD's description of the Chen study has been re-written to improve its clarity. The relative enzyme induction potencies found for BaP and diesel exhaust actually show that BaP is much more potent as an inducer of AHH activity than is diesel exhaust extract. The commenter is correct that the weight percentage cited in IARC (1989) is 9%. The TSD no longer cites a weight percentage here.

AHH induction is one of the most commonly used biomarkers of exposure to PAHs, dioxins, and a number of other toxins. AHH induction is observed with exposure to most if not all PAHs; induction of AHH activity-by diesel exhaust particulate matter suggests that PAHs in diesel exhaust particulate matter are bioavailable. Since PAHs are highly toxic, and AHH induction likely indicates that PAHs are bioavailable, AHH induction may be indicative of a strong potential for adverse health effects, even though the enzyme induction is not itself an adverse effect. The TSD's discussion of the Chen et al. (1986) study now states that AHH induction is not, by itself, an adverse effect; this is the appropriate interpretation of AHH induction studies.

14. Comment summary: The role of injection studies in evaluating the effects of diesel fuel should be qualified by indicating that these studies do not represent environmentally relevant exposure routes and that extrapolation of the results of these studies to the inhalation route of exposure is very uncertain. (p. 3-5)

Response: Only inhalation studies were used in the extrapolation of animal results to humans. The studies using the intratracheal route are mentioned because the resultant effects observed are toxicologically relevant despite the difference from conventional environmental exposures. Furthermore, the exposures, though unconventional, are not irrelevant to the actual environmental situation. The intratracheal studies are not technically "injections", but are

applications of material (in this case, diesel exhaust particles) with a blunt dispenser directly into the tracheal region. The exposure bypasses the nasal filtration that occurs in inhalation experiments. Intraperitoneal injections, by contrast, are not environmentally relevant exposures, but the studies do provide information leading to the understanding of mechanistic bases for the effects diesel exhaust particles have on metabolism and other systemic functions.

15. Comment summary: The inhalation study of Prasad et al. 1988 cannot be interpreted as to the effects of diesel particulate on phagocytic activity since an acid-only treatment group was not tested. The discussion of the study should thus be qualified. (p. 3-5)

Response: The Prasad et al. report states (on page 387) that the aim of the exposure was "to simulate an environmental exposure to a complex carbon-acid atmosphere during an extended air pollution episode." The exposure, though not purely comprised of diesel exhaust, was environmentally relevant. For comparison, the 7-component mixture also tested by Prasad et al., though not an optimal control, yielded negative results on phagocytosis. We have added a sentence to the TSD to indicate the absence of an "acid-only" control, as suggested by the comment.

16. Comment summary: The middle exposure level in Strom et al. (1984) was 0.75 mg/m^3, not 0.25 mg/m^3 as reported on p. 4-6 of Part B. (p. 3-5)

Response: We have revised the document accordingly.

17. Comment summary: It is not clear what criteria, if any, were used to select the studies for description in the chronic exposure section of Part B. (p. 3-5)

Response: The chronic animal studies discussed in the TSD were chosen because of their long duration of exposure to diesel exhaust (greater than 6 months, see Section 4.2.4). The human epidemiology studies were chosen because of their direct or implied evidence of exposure to diesel exhaust.

18. Comment summary: OEHHA appears to attribute the lack of positive carcinogenicity results in hamster studies of diesel exhaust to resistance to increases in DNA adduct formation. This statement appears to be contrary to the overriding conclusion that the carcinogenicity of high levels of exposure to diesel exhaust is primarily associated with chronic inflammation. (p. 5-1)

Response: OEHHA staff have not found an overriding conclusion that the carcinogenicity of high levels of exposure to diesel exhaust is primarily due to chronic inflammation. Regarding the hamster study results, the TSD notes the association between the lack of DNA adducts and the lack of increased tumor incidence in the studies. The TSD does not attribute the lack of positive carcinogenicity results in hamster studies of diesel exhaust to resistance to increases in DNA adduct formation. The document (Part B, Chapter 5) merely notes that "the species differences in the incidence of adduct formation and the location of adducts within the respiratory tract are consistent with the pattern of tumor formation in exposed animals." It should be clear to the reader that no causal inference is intended.

19. Comment summary: The mouse studies discussed in Section 6.1.1.1 of Part B may all be regarded as deficient, particularly since no study tested more than one concentration of diesel exhaust particulate and because only levels of exposure of diesel exhaust known to cause lung overload were tested. (p. 5-1)

Response: The mouse carcinogenicity bioassays described in Chapter 6 were generally of appropriate design to investigate a possible association between inhalation exposure to diesel exhaust and increased tumor incidence in mice. Unit risk values were not derived from mouse tumor data. Additionally, the TSD has been revised to discuss studies by Heinrich et al. (1995) and Mauderly et al. (1996) which tested multiple exposure concentrations of diesel exhaust in mice.

20. Comment summary: The document reviews studies of the carcinogenicity of diesel exhaust in rats that are remarkably consistent in the observation of no carcinogenic effects at adjusted exposure levels less than or equal to 0.57 mg/m^3 (adjusted for lifetime exposure, 24 hours per day) and late appearance of the majority of the lung tumors. (p. 5-1)

Response: Increased lung tumor incidence has not generally been noted in rats exposed to diesel exhaust concentrations of less than 2. 5 mg/m^3 (unadjusted) . However, since the chronic rat studies do not allow for direct examination of effects at low doses due to limitations in the power of the studies to detect low-incidence effects, it is not possible to ascertain the existence of a threshold from these data. All malignant tumors, including those appearing late in the test animals' lives, are included in the TSD's quantitative risk assessment.

21. Comment summary: The TSD alludes to a theory of an "unknown strongly carcinogenic substance" that may possibly account for the carcinogenic potency of diesel exhaust. However, a study reviewed in the document examined the potential carcinogenicity of diesel exhaust condensate in rats. The 4-7 ring PAH subfraction was responsible for most of the carcinogenic activity. Given the findings of this study, it seems unlikely that some "unknown strongly carcinogenic substance" or, as alluded to in the document, nitro-PAH compounds, is primarily responsible for the carcinogenicity of diesel exhaust in rats. It could also be argued that such an "unknown strongly carcinogenic substance" could be present in the vapor phase of diesel exhaust. However, this theory would not be well supported given the negative results of certain studies reviewed in the document. (pp. 5-1 - 5-2)

Response: In the study referred to in the comment (Grimmer et al., 1987), the carcinogenicity of fractions of diesel exhaust obtained by a special condensation and filtration method was examined. It is possible that an "unknown strongly carcinogenic substance" could have been artifactually eliminated by the fractionation process. Previously, unknown mutagenic and/or carcinogenic nitro PAHs have been discovered in diesel exhaust (Sera et al., 1994). Additionally, there are several studies containing positive bioassays of filtered diesel exhaust. These are described in Chapter 6 of Part B.

22. Comment summary: The commenter agrees that particle overload and the resulting inflammation and cell turnover in the lung are the likely explanations for the carcinogenic

activity of diesel exhaust in rats. Although not directly discussed in the TSD, the relatively lower degree of lung inflammation observed in hamsters may also explain the lack of carcinogenicity of diesel exhaust in hamsters. While it may be argued that inhibition of particle clearance from the lung occurs more readily in the rat than in the hamster, a species difference in inflammatory response is a reasonable alternative hypothesis to explain the relative resistance of the hamster to the carcinogenic effects of diesel particles. (p. 5-2)

Response: The TSD discusses increased chronic inflammation and cell proliferation in the lung as being potentially mechanistically involved in the carcinogenic activity of diesel exhaust in rats. However, the TSD also notes a potential role for genotoxic mechanisms.

Although investigators have conducted three studies of diesel exhaust inhalation and lung cancer in hamsters (these are described in the TSD), OEHHA staff do not generally consider the hamster to be a useful model for qualitative or quantitative risk assessment of potential human lung carcinogens. In reporting their negative findings with diesel exhaust, Heinrich et al. (1986) pointed out that "contrary to the rat," hamsters have "failed to develop lung tumors ... after inhalation of high concentrations of pure BaP [benzo(a)pyrene or even cigarette smoke, a well known human carcinogen." Ten years later, the International Agency for Research on Cancer (1996) specifically addressed the relative strengths and weaknesses of the hamster model for different tumor types. IARC, too, noted that there have been no reports of lung tumor development in hamsters due to inhalation of benzo(a)pyrene or cigarette smoke. IARC stated that even with radionuclides it is difficult to induce lung tumors in hamsters, except with intratracheal instillation of polonium-210. Nickel and silica were both negative in hamsters upon inhalation or instillation. Instillations of glass fibers and asbestos have yielded mixed results. The insensitivity of the model indicates that hamster data should not be considered valid predictors of human lung cancer risk. Thus the TSD does not present quantitative risk estimates based on the hamster data.

23. Comment summary: The results of Lewis et al. (1986) suggest that the rat may not be the most appropriate model for estimating the possible pulmonary effects of diesel exhaust in man, particularly when it is considered that the monkey, a species generally believed to be the most like humans, did not develop inflammatory lung changes under the identical exposure conditions found to produce inflammatory lung changes in rats. (p. 5-2)

Response: The revised TSD (Section 4.2.3) includes a discussion of the Lewis et al. (1986) study in monkeys and rats. The reasons for not selecting data from the monkey model for the purposes of determining a quantitative non-cancer risk value for diesel exhaust are discussed in Section 4.2.4. Lewis et al. (1986) exposed monkeys to diesel exhaust for 2 years. Results of the study included a significant increase in mild pulmonary acute and chronic inflammatory responses at the one dose tested, 2 mg/m^3. In addition, diesel-treated monkeys all exhibited small airway obstructive disease, as measured by decreased maximal expiratory flow rate after 6, 12, 18, or 24 months. This study does not settle the issue of whether the monkey or the rat is a better model for the pulmonary effects of diesel exhaust in humans. The study offers no comparison with effects in humans. In practical terms, the monkey will probably not serve as a good model for diesel exhaust-induced cancer due to the cost and other difficulties involved with performing lifetime

studies with this species. The monkey might serve as a good model in the absence of these difficulties, yet the findings of Lewis et al. do not obviate the usefulness of the rat model.

24. Comment summary: The commenter agrees that epidemiologic studies should be rigorously examined before concluding that a substance is carcinogenic to humans. However, the commenter strongly disagrees with Cal/EPA's assessment that these studies have provided adequate evidence of the carcinogenicity of diesel exhaust in individuals with occupational exposure. As noted in the Cal/EPA's draft document, the studies have significant weaknesses.

The most significant weakness of these studies is the complete lack of exposure data regarding diesel exhaust or other substances. Even the occurrence of significant diesel exposure among study populations in many of the cited studies is questionable. The second significant weakness of these studies is the lack of data regarding cigarette smoking. It is not surprising that individuals in occupations associated with potential diesel exhaust exposure have a higher rate of lung cancer than the general population since they also have higher rates of smoking.

Another consideration in examining these data are the effects of passive cigarette smoke. While the carcinogenicity of "environmental tobacco smoke" (ETS) is a subject of controversy, the relative risk reported in the studies of diesel exposure cited by Cal/EPA are within the range of risks usually given for ETS. The high smoking prevalence rates noted in several of the epidemiologic studies are consistent with significant exposure to ETS. The 20 cited studies available to this commenter in English did not examine the possible confounding effects of ETS. Over half of these did not even perform a cursory examination of smoking history among the participants.

The third major weakness of the cited epidemiologic studies is that the relative risks are almost all below 2.0. The significance of relative risks of this magnitude is highly questionable since it is nearly impossible to control for and exclude the contribution of various identified or unidentified confounders. The most obvious confounder is smoking. There are several other weaknesses associated with the cited epidemiologic studies. These include: reliance on death certificate data for cause of death which may not be accurate; reliance on death certificate data for occupation which may only reflect the last occupation of the deceased and provides no data on occupational history; failure to consider latency effects; no histological confirmation of primary lung cancer or cell-type; reliance on next of kin for information regarding smoking or occupational history; multiple comparisons; incomplete case ascertainment; and inadequate sample sizes. (pp. 5-3 - 5-5)

Response: Regarding whether diesel exhaust is a human carcinogen, the TSD thoroughly evaluates the increased relative risks of lung cancer observed in the epidemiologic studies and their association with diesel exhaust exposure. In support of this conclusion the revised Part B includes a meta-analysis of occupational studies. Some of the studies have weaknesses and some, especially the Garshick et al. (1987a, 1988) studies, are strong.

The TSD's meta-analysis provides a strong indication that confounding factors such as smoking are not responsible for the excess carcinogenicity observed in diesel exhaust-exposed

occupational groups. The meta-analysis increases confidence in the positive findings of studies with relative risks below 2.0.

Good measurement-based estimates of exposures to environmental tobacco smoke (ETS) and other respirable particles were obtained for railroad workers. The exposure measurements in Woskie et al. (1988a,b) and Hammond (1988) specify a value for the level of ETS exposure of each the major types of railroad worker. The clerks had the highest value, so using that group as the reference group (the group not exposed to diesel exhaust), as did Garshick et al. (1987a, 1988), would make ETS reduce the observed potency of diesel exhaust below its true value, if ETS affects the observation at all. Thus in this case there is no reason to believe that the finding of diesel exhaust-associated carcinogenicity was a spurious result produced or exaggerated by ETS. In fact, some of the effect might have been masked by ETS. As suggested in the comment, measurements are not available to us in other cases.

The comment suggests other weaknesses associated with the cited epidemiological studies. There is no suggestion of what the effects of these alleged weaknesses might be. In particular no resulting bias is claimed even though each point does introduce some uncertainty about a possible effect. For example, the first point is about potential inaccuracies in cause of death in the death certificate. There is no evidence or available argument to suggest that any misclassification of cause of death would indicate a greater proportion of false lung cancer cases in the exposed than in the unexposed group. Similarly there is no available evidence that any of these other alleged weaknesses actually affected the results, especially given the consistent results of the meta-analysis.

25. Comment summary: Although Cal/EPA has cited the railway worker studies as the primary evidence that diesel exhaust exposure is associated with lung cancer, the railway worker studies provide no support for a causal association between diesel exhaust exposure and lung cancer.

The designation of Kaplan et al. (1959), a negative study, as "uninformative" is inaccurate. Some considerations were overlooked. While the study participants may not have been exposed solely to diesel exhaust, they were exposed to fumes from the burning of other fuels. These fuels contain much of the same combustion products as diesel exhaust as well as arsenic and other substances. The results suggest that these types of combustion products are not associated with lung cancer at the levels typically encountered by railroad workers. Further, the study was conducted during a period when the health effects of smoking were less apparent. One could argue that it may be less confounded by smoking than later studies.

With regard to Howe et al. (1983), Cal/EPA has stated that "in view of the fact that there is evidence from animal and human studies for the carcinogenicity of diesel fumes but such evidence does not exist for coal dust, it seems most likely that the apparent effect of coal dust was due to confounding with diesel exhaust, rather than vice-versa." This is unsupportable since 1) the carcinogenicity of diesel fumes in humans has not been established; 2) the exposures associated with "coal dust" are unclear (i.e., dust, combustion products etc.); 3) there was no analysis of levels of smoking in the various exposure classifications; and 4) levels of exposure are completely speculative. The most likely explanation is that diesel and coal dust exposure

were confounded by smoking. Because the study has extremely limited information, it cannot support a relationship between diesel exhaust exposure and lung cancer.

The 1987 case-control study report by Garshick et al. of lung cancer in railroad workers has significant limitations and cannot support a causal association between diesel exhaust exposure and that cancer.

The TSD suggests that the Garshick et al. (1988) cohort study is evidence of a dose-response relationship. Disregarding the fact that smoking was not even examined and the levels of exposure among the study population are purely speculative, the difference between the relative risks for the different exposure groups are less than 1.0. The confidence intervals for the groups with the most years of exposure are much wider than for the other groups. Thus, it is difficult to conclude that this represents any kind of dose-response relationship. The findings after elimination of the shopworkers from the analysis (relative risks increased, although studies indicate that these workers were the highest exposed) are further evidence that a dose-response relationship does not exist. (pp. 5-5 - 5-11)

Response: Regarding whether diesel exhaust is a human carcinogen, the TSD thoroughly evaluates the increased relative risks of lung cancer observed in the epidemiologic studies and their association with diesel exhaust exposure. In the current draft TSD, criteria for causal inference are discussed in Section 6.2. The railroad worker studies are one of the stronger elements in the new meta-analysis.

It is difficult to see how the early exposures of the workers in the study of Kaplan et al. would offer any useful comparison to diesel particles because of the much larger sizes of other kinds of particles in the exposures mentioned in the comment. Arsenic is a known carcinogen, but the amount reaching cellular targets may have been negligible.

In regard to the remark on the study of Howe et al., 1) carcinogenicity of diesel exhaust has been acknowledged by the International Agency for Research on Cancer, among others, 2) probability of exposure to coal dust was obtained in the study, 3) there are no estimates of the level of smoking, and 4) probabilities of exposure were obtained in the study. Concerning points 2) and 4), random errors in assignment of probabilities would tend to bias the result toward no effect. Finally, the comment does not provide support for the assertion that smoking offers the most likely explanation for the increasing trends of lung cancer with probability of exposure to both diesel exhaust and coal dust.

The comment gives no specific limitations here as a reason for dismissing the Garshick et al. case control study.

Notwithstanding the lack of direct measurement of smoking in the Garshick et al. (1988) cohort study, investigators (Cohen and Higgins, 1995) have stated that the elevated relative risk found in this study could not be explained by cigarette smoking. The argument refers to data from the Garshick et al. (1987) case-control study as evidence of lack of confounding due to smoking in

the cohort study of the same workplace. The case-control study obtained smoking habit data from some next of kin by questionnaire.

The analysis of the Garshick et al. cohort study in the revised TSD has been modified to exclude shopworkers. That job did have some very highly exposed workers and also some workers with virtually no exposure, but the actual proportion of exposed-to-unexposed is not known. Hence the exclusion. The revised TSD shows that, due to their very heterogeneous exposure, the overall risk of shopworkers is most likely to be about the same as for train workers. On this basis, the very small reduction of risk with shop workers removed, as reported in Garshick et al. (1988), is well within the random variation of the data. It is correct that the apparently most highly exposed group had the widest confidence interval. This reflects the choice of category boundaries that resulted in less cancer deaths in that group. Although the maximum likelihood estimates of relative risk are all below 2, the three highest exposed groups were all just significantly above 1. Moreover, the trend is statistically significant. In sum, the cancer slope factors calculated from Garshick et al. (1988) are based on valid assumptions and are themselves valid representations of overall slope.

26. Comment summary: A 1984 study of Finnish locomotive drivers by Nokso-Koivist and Pukkala was not considered in preparation of the TSD, but its findings are relevant for interpreting the U.S. studies. It had less potential for confounding by smoking than the U.S. studies. Lung cancer rates in the Finnish drivers were similar or less than that of the Finnish general population and did not appear to be affected by potential diesel exhaust exposure. Cal/EPA should consider the following implications of this study in interpreting the U.S. railroad studies: 1) it is likely that the prevalence of smoking among locomotive engineers in the steam engine era was less than in the diesel era due to working conditions and job requirements; 2) there appears to be little difference between exposures to combustion products (e.g., benz[a]pyrene) from steam or diesel engines; 3) exposures in diesel locomotives are not much higher than those experienced by the general population; and 4) working conditions in the diesel locomotives would also likely promote higher levels of ETS. (pp. 5-11 - 5-12)

Response: OEHHA staff thank the commenter for calling attention to this study. An account of this study is now included in Part B's Section 6.2 and it is used in the meta-analysis of Appendix D. It is not clear that this study had less potential for confounding by smoking than the U.S. studies. If the Finnish drivers smoked less than the general population, then that would obscure the effect of diesel exhaust on the standardized rates. (1) The effect of an obscure possible increase of smoking rate with time is difficult to assess. (2) Steam engine emissions would be expected to produce much larger particles than diesel engine emissions, implying a different impact on the lung. (3) If exposure to diesel exhaust in the diesel engines is very small, then that also would account for seeing no effect on lung cancer. No evidence in the comment is offered concerning the levels of exposure to diesel exhaust. (4) Working conditions in the diesel locomotives could produce higher levels of ETS than in the steam locomotives but may actually produce lower levels than in many other enclosed places. The comment offers no data on this. See also response to Comment 5.

27. Comment summary: The TSD notes that there is "a considerable degree of consistency in regard to a finding of elevated lung cancer rates in workers believed to have been exposed to diesel exhaust." However, it should be noted that 13 of 23 (57%) cited studies were of truck drivers. Cal/EPA has noted that 1) most of the truck driver studies had no information on smoking; 2) truck drivers smoke more than the general population; 3) truck drivers may have additional exposure to cigarette smoke through rebreathing smoke or high passive smoking exposure in the truck cabs; and most importantly 4) as Cal/EPA notes, "there is little evidence that truck drivers have actually been greatly exposed to diesel emissions, although the presumption that they have is frequently made." The study by Boffetta found no difference in lung cancer risk between drivers with diesel exposure and those without exposure. Thus, the truck driver studies should not be used as evidence of an association between diesel exposure and lung cancer. Similarly, the studies of the transport and dock workers included many workers unlikely to have had diesel exhaust exposure although these workers are known to have high smoking prevalence rates. Only one of the transportation and dock worker studies examined smoking and these data were incomplete.

Of the three railroad studies used to support an association between lung cancer and diesel exhaust exposure, only one actually examined smoking prevalence in the study population. Thus, by Cal/EPA's own definitions, only one study (the Garshick et al. case-control study) was complete enough to examine a possible relationship. This hardly constitutes a "considerable degree of consistency" in findings.

The TSD correctly notes that the most likely form of bias affecting the epidemiologic studies is confounding by cigarette smoking. Garshick et al. (1987a) has been cited by Cal/EPA as having best accounted for the confounding effects of smoking. However, the prevalence of smoking in the lung cancer cases in this study was over 90%. Diesel exhaust exposures were unknown in the study participants. The exposure category for smoking used to derive the relative risk was >50 or <50 pack-years. A total of 50 pack years is obviously a very significant smoking history and is not a sensitive control for smoking. Also, pack year history was missing for approximately one-quarter of the study population which introduces a significant non-response bias. This or other unidentified confounders could easily explain the reported relative risk of 1.41 for workers less than 64 years of age. Thus, Cal/EPA has not presented any epidemiologic evidence which satisfactorily excludes smoking as a cause for the slightly elevated risk ratios.

Cal/EPA states that exposure misclassification in the studies may have occurred but that the misclassifications would tend to bias the results towards unity. However, it is evident from studies of smoking prevalence rates in various occupations that the occupations classified as diesel-exposed also tend to have higher smoking prevalence rates. Based on the lack of data regarding diesel exposure levels in the cited studies, it can be argued that these studies do nothing more than identify groups with higher smoking rates. Without adequate control for smoking, the classification system introduces a significant source of systematic bias.

Cal/EPA has correctly noted that evidence of causality is weakened by the low risk estimates which are less than 2. When considering the fact that none of the studies adequately controlled

for smoking and that levels of diesel exposure were not known in any of the studies, the association of lung cancer with diesel exposure cannot be justified.

Cal/EPA has cited four studies (3 railroad studies plus Boffetta et al. 1988) as evidence of a dose-response relationship. However, two of these studies did not even examine smoking history among the study population. The two others found smoking prevalences of over 90% in the lung cancer cases. None of the studies had a numerical estimate of diesel exhaust exposure levels in the study population. Exposure to diesel exhaust has been based on speculation. Thus, Cal/EPA has not presented evidence which supports a dose-response relationship.

Although the TSD notes that Boffetta et al. (1988) reported a dose-response between two groups by number of years of exposure (1-15 years and 16+ years), the risks of lung cancer in the two groups were not significantly different from unity. Based on the test for trend, there was not a significant difference between the risk ratios for the two groups. In a case control study published two years later, Boffetta et al. (1990) noted that all of the diesel exhaust studies (including their analysis which controlled for smoking) are consistent in failing to reveal an association." In reviewing the same studies of railroad workers cited by Cal/EPA they concluded "no firm evidence of an excess lung cancer risk from diesel exhaust exposure among railroad workers has been provided."

Cal/EPA notes that the association of diesel exposure with lung cancer is "highly biologically plausible" based on the ability to induce lung and other cancers in laboratory animal studies. Results of these studies cannot necessarily be extrapolated to humans, particularly in view of the relative exposure levels and methods of administration in the animal studies as compared to humans. There is evidence of prerequisite inflammatory changes and alterations in lung clearance mechanisms that must occur before lung tumors are induced by diesel exposures. A threshold effect for carcinogenicity in the animal studies is apparent which is considerably higher than the levels likely to occur in occupationally-related exposure. Thus, it is questionable whether an association is highly biologically plausible.

This commenter has reviewed the studies cited by Cal/EPA and does not agree that evidence has been provided for a causal relationship between diesel exhaust exposure and lung cancer. The commenter disagrees with the statement that "the many associations found between lung cancer and diesel exposure are unlikely to be due to chance" because the "many associations" were based on flawed methodology in which the extent of diesel exposure is totally unknown and smoking has not been adequately examined. The commenter disagrees with the statements that the findings "are unlikely to be due to bias" and that "three key studies show clear dose-exposure relationships" since these three studies have serious flaws. The conclusion that "the evidence is sufficient that diesel exhaust contributes to human cancer" cannot be supported by the studies cited. (pp. 5-12 - 5-14)

Response: Chapters 1 and 6 of the revised TSD now clarify the relationship between elevated, although not always statistically significant, lung cancer risks in workers and potential exposure to diesel exhaust within several industries. The meta-analysis in the new draft TSD properly enumerates the truck driver studies. The meta-analysis allows for the consideration of the truck

driver studies and the other studies in spite of potential uncertainties mentioned in the comment. The revised TSD describes the study of Boffetta et al. (1988) more extensively than the 1994 draft TSD.

The Garshick et al. (1987a) case-control study examined the smoking issue. The study was designed and analyzed to minimize the possibility of confounding. The comment suggesting that confounding may have occurred because of high smoking rates does not develop any analysis of how this might have occurred. In regard to the hypothesis that the diesel-exposed workers may smoke more, thus accounting for higher lung-cancer rates, there is no direct evidence for this in the studies reviewed, and in some studies a dose-response relationship was obtained or at least suggested, making reference to external populations unnecessary.

The TSD now includes a meta-analysis of the epidemiologic studies which quantitatively evaluates the overall significance of a group of studies. The meta-analysis provides a strong indication that confounding factors such as smoking are not responsible for the excess carcinogenicity observed in diesel exhaust-exposed occupational groups. The meta-analysis increases confidence in the positive findings of studies with relative risks below 2.0.

The Woskie et al. (1987a,b) studies directly apply to the two railroad worker studies by Garshick et al. (1987a, 1988). These studies can thus give evidence for a dose-response relationship, as developed in Part B's Chapter 7.

With regard to biological plausibility, the revised Part B does not rely solely on the results of the rat studies. Nevertheless, these studies provide an indication that a similar carcinogenic response can occur in humans.

OEHHA staff disagree that the many associations found and the studies showing dose-response relationships were based on flawed technology and disagree that smoking has not been adequately examined. Regarding whether diesel exhaust is a human carcinogen, the TSD thoroughly evaluates the increased relative risks of lung cancer observed in the epidemiologic studies and their association with diesel exhaust exposure.

28. Comment summary: Data in the rat show that impairment of lung clearance resulting from chronic exposure to diesel exhaust is a threshold phenomenon. This apparent threshold occurs at exposures below those shown to induce lung tumors in this species, but above exposures required to induce an inflammatory response. Any assessment of risk for low-level human exposure to diesel exhaust should account for threshold effects that are likely to be associated with occurrence of tumors. Mathematical modeling of rat tumor data should include non-zero dose and latency values in the model. (pp. 6-1 - 6-7)

Response: The mechanism of action by which diesel exhaust induces lung tumors in rats is not established. One proposed mechanism is that exposure to diesel exhaust particulate matter at high concentrations exceeds pulmonary clearance capabilities and causes chronic inflammation. This inflammation leads to macrophage and/or neutrophil-induced oxidative DNA damage resulting in mutations which are instrumental in the induction of lung tumors, and also leads to cell

proliferation which may be mechanistically important to the promotion of the rat lung tumors. This mechanism may have an exposure threshold of action. However, the possibility that genotoxicity due to the PAH and nitroPAH content of diesel exhaust plays a role in the induction of lung tumors in rats at lower levels of diesel exhaust cannot be excluded. This mechanism would probably be relevant to human cancer risk, and would not be expected to have a threshold of action. (Chapter 5 of Part B describes the extraction under physiological conditions of mutagens from diesel exhaust, as well as increased lymphocyte DNA adducts in humans occupationally exposed to diesel exhaust.) In addition, the proposed overload mechanism includes chronic inflammation and associated production of inflammatory cytokines and increased cell proliferation. As noted in a recent paper by Gaylor and Zheng (1996), (1) a threshold dose is questionable if a carcinogen acts via a cell receptor, (2) even a nongenotoxic carcinogen that increases the cell proliferation rate by augmenting an endogenous mechanism is not likely to have a threshold dose, and (3) dose response curves for cell proliferation and tumor incidence do not necessarily mimic each other. The rat lung tumor data are not irrelevant to human cancer risk from diesel exhaust.

The TSD's quantitative analyses include the use of the Moolgavkar model, which does not force the threshold to equal zero. As described in Chapter 1, there is no clear indication of a threshold for carcinogenesis.

29. Comment summary: The use of all lung tumors instead of malignant tumors is one of seven principal areas in which assumptions and quantitative procedures used in the TSD exaggerate the animal-based risk projections. (The other areas are summarized below.) The endpoint used to estimate the unit risk includes benign tumors and malignant tumors (cancer). Because the endpoint included benign tumors, the 95% UCLs given in the document are 95% UCLs on unit risk of any lung tumor and not unit risk of malignant tumors (cancer). The use of benign and malignant tumors instead of malignant tumors only as the definition of a response inflates the estimates of cancer risks by at least four orders of magnitude. (pp. 6-8, 6-9 - 6-10)

Response: The benign tumors, squamous cysts, have been removed from the risk assessment's count of neoplasms, which are the tumors of concern. This removal reduces risk estimates by approximately 30%. The other benign tumors, adenomas, remain in the count of neoplasms because of evidence that adenomas can progress to a malignant tumor, adenocarcinoma.

30. Comment summary: In forcing the dose threshold to equal zero, the TSD exaggerates the animal-based risk projections. Cal/EPA estimated the unit risk using the multistage-Weibull model and the two-stage model (Moolgavkar et al. model). The TSD claims that the estimates of the dose thresholds and latency periods in the models are all zero. The zero thresholds on dose and zero latency periods were only explicitly reported for the Moolgavkar model and when that model was fit with an incorrect time scale. However, if the dose thresholds and latency periods are estimated for some other models (multistage and multistage-Weibull models) and the correct time scale (age as opposed to exposure duration), the data seem to indicate the existence of a dose threshold well beyond the concentration of concern (3.7 $\mu g/m^3$) . Because the estimated human threshold doses are well above the human exposure concentrations, the added risks of diesel exposure are zero when the multistage model and the multistage-Weibull model are fitted

using a threshold dose. The existence of threshold doses for the effects of diesel exposure is not contradicted by the results obtained by Cal/EPA for the Moolgavkar model and all lung tumors as their response of interest. Although the maximum likelihood estimate of the threshold dose obtained by Cal/EPA in this case was zero, the value of the likelihood function which was being maximized in the maximum likelihood estimation procedure was not significantly different from the likelihood function values corresponding to several threshold doses substantially greater than zero. (pp. 6-8, 6-10 - 6-11)

Response: The 1994 TSD (p. 7-4) reports that all four of the calculations gave a latency period of 0. This was an MLE result. The dose threshold of 0 was also an MLE result for the Moolgavkar model. For the multistage Weibull model, the TSD assumed no dose threshold, which is the usual form of the Weibull model, as in TOX_RISK. The commenters calculation of their nonzero value for a threshold does not have any account of the uncertainty of such an estimate. This value is the horizontal location of a line with low slope, a mathematical procedure that is not expected to give an estimate that is likely to be meaningful. This sort of mathematical uncertainty, which the commenters allude to in the TSD finding of zero dose threshold for the Moolgavkar model, is a part of the reason for choosing no threshold for such models. Another is that potential genotoxicity is expected to be present at all doses above zero.

31. Comment summary: The use of inappropriate time in time-to-response model prediction of human risks causes the TSD to exaggerate the animal-based risk projections. In fitting the Mauderly et al. rat data, Cal/EPA used time-to-response data, with weeks of exposure as the time. The TSD assumed that the median lifespan of female rats (131.7 weeks, 17 weeks prior to exposure and 114.7 weeks of exposure) is equivalent to a human lifetime (70 years). Then, to estimate the 95% UCLs on unit risk, the fitted models in Cal/EPA's report were evaluated at 131.7 weeks. The choice of the female median lifespan (131.7 weeks) as opposed to the male median lifespan (129.6 weeks) increased the UCL on the unit risk. However, more importantly, the 131.7 weeks that was assumed to be equivalent to 70 years of human lifespan was age and not exposure duration. The fitted models should have been evaluated at an exposure duration of 114.7 weeks, not 131.7 weeks, because the "time', in the time-to-response models was exposure duration (not age). The net effect of this erroneous substitution of 131.7 weeks for 114.7 weeks is an inflation of the calculated 95% UCL on unit risk. The magnitude of the inflation caused by substituting the wrong time varies depending on the model and the parameter estimates. It is roughly a two-fold exaggeration. A source of uncertainty in the extrapolation of animal risks to human risks is the extrapolation from intermittent exposure starting part way through life to continuous exposure from birth. Risks are estimated using a lifetime average daily dose. The data are fit using the environmental exposure that started at age 18 weeks and lasted 7 hours per day, 5 days a week, and 134 weeks. Humans are assumed to be exposed to a diesel exhaust concentration 24 hours a day, 7 days a week, during their entire lifetime. If risks are to be estimated in terms of a lifetime average daily dose, then the animal doses should be converted to lifetime average daily doses before the model is fit to the data, and the 4.8 exposure extrapolation factor should then be eliminated when estimating added risks. (pp. 6-8, 6-11 - 6-12, 6-18 - 6-19)

Response: In regard to the commenters' assertion that the TSD used an inappropriate rat lifetime to extrapolate to humans, the detailed reasoning for the TSD is as follows: Mauderly et al. (1987,

p. 211) state that the median time of survival of control rats with both sexes combined is 922 days, which is 131.7 weeks. The commenters do not reference the source of their values. The TSD uses this value as the best available estimate for these rats' lifetime that would correspond to the human target lifetime currently used in regulatory risk assessments. The computations that give the coefficients of the cumulative hazard function, Eqs. 7-2, 7-3, do not use any information on lifetime. For each rat that dies, the computations simply use the information on duration and concentration of the constant exposure, which starts following the 17th week of the rats' life. Once the coefficients are calculated, the risk for that kind of rat at any constant exposure is predicted by using those coefficients and the concentration and duration selected - in this case 1 $\mu g/m^3$ and 131.7 weeks, to approximate the corresponding human situation. There is, according to this model, no need to refer to how the coefficients were obtained. The TOX_RISK program structure follows this dichotomy of experimental determination and target prediction.

The commenters correctly identify the conversion from intermittent to continuous exposure as a source of uncertainty. However, their statement that the true dose should be used in fitting the model to the data, thus eliminating the application of the intermittency factor of 4.8 at a later time, does not reduce the uncertainty. Although there is a case for the commenters' approach being a little clearer theoretically, the conversion of dose before is mathematically equivalent to changing after, like changing between grams and pounds. The TSD approach was in practice a little simpler computationally.

32. Comment summary: Assumptions regarding time-to-response model selection and parameterization cause the TSD to exaggerate the animal-based risk projections. The TSD examines two time-to-response models: the multistage-Weibull model and the Moolgavkar model. Although time-to-response models can incorporate more of the experimental animal data, their use in risk assessments should reflect the underlying properties of time-to-response models.

The time-to-response models used by Cal/EPA do not incorporate competing risks (like heart attacks, accidental deaths, etc.). Thus, the resulting estimates of added risk due to diesel exhaust assume that "all" humans live to be 70 years old. This assumption overestimates the added lung cancer risk due to diesel exhaust. The overestimation occurs because a significant percentage of the population normally dies before age 70 and is not subject to any lung cancer hazard rate associated with diesel exhaust for a full 70 years.

In the TSD's parameterization of the Moolgavkar model there is significant interaction between two parameters. This means that there are several combinations of these parameters that result in the same model value for a given dose. The interaction between these parameters makes the maximum likelihood estimation equivocal in the sense that there may be more than one set of parameter values that maximize (or approximately maximize) the likelihood function. The parameter interaction gets worse when the threshold in dose and the latency period in time are included in the estimation. These interactions have at least two major consequences. First, the presence or absence of a threshold in dose or a latency period in time should be evaluated by considering alternative fixed values for these parameters and determining whether or not the corresponding value of the likelihood function is sufficiently near the maximum likelihood value. Second, high-to-low extrapolations for some combinations of parameter values (particularly

those involving high powers of dose) may be very sensitive to the numerical properties of the computer program implementing the model and should be carefully scrutinized. Other parameterizations would be better. The TSD's parameterization of the multistage-Weibull models contains some interaction among its parameters, but this is much less important than the problems that high-to-low-dose extrapolations could cause due to interaction among parameters in the Moolgavkar model. (pp. 6-8, 6-12 - 6-16)

Response: Yes, the lack of inclusion of competing risks in the models of the TSD does give the pure rat-based risk and not what would be observed in the real human population with more competing causes of death than in the isolated rats. Because 70 years is a substantial underestimate of human lifespan, the use of that value in the calculations tends to offset the more health protective assumption of equal competing causes of death.

The commenters do go on to suggest another parameterization, which has a small effect on the risk calculations. Their Tables 6-3 to 6-26 give results which allow comparison of using the TSD parameterization of the TOX-RISK program to using their restricted polynomial parameterization. The TSD parameterization generally yields the higher risk, but the values are often within a few percent and rise only to two-fold or a bit more.

33. Comment summary: The methodology used in the TSD to calculate upper bounds causes exaggeration of the animal-based risk projections. Although Cal/EPA claims that the ratio of 95% UCL to MLE unit risks is between 1.5 and 5 when the all lung tumor data are used, this ratio is several orders of magnitude larger if only malignant tumors are considered as the response. However, the 95% UCL on q_1, when the linearized multistage model is applied to the malignant tumors only is 8 orders of magnitude larger than the maximum likelihood estimate for air concentration and 17 orders of magnitude larger for lung burden.

Another practical problem with the upper bounds generated by the linearized multistage model is that the model's 95% UCLs are insensitive to the observed data. For example; despite the differences in the dose-response relationships for all lung tumors as opposed to malignant tumors, the linearized multistage model's 95% UCLs based on all lung tumors were only 3 to 4 times larger than the model's 95% UCL based on malignant tumors.

The use of the specific confidence limit procedure in the "linearized" version of the multistage-Weibull model and the Moolgavkar model to estimate a 95% upper confidence level on the risk may also exaggerate the 95% UCL in comparison to an alternative procedure's upper bound. The problem with the linearized procedure is that it is designed to "work" (that is, generate a bound on the risk that is greater than or equal to the true risk) at least 95% of the time for any underlying set of parameter values for the model. This means that the bounding procedure must work 95% of the time for parameter values which would imply a linear model even though the true parameter values may imply a sublinear model. In terms of trying to determine upper bounds on the risks at low doses by extrapolating from observed high doses down to low doses, it is tougher to exceed a slowly decreasing risk (a linear model) than a more rapidly decreasing risk (a sublinear model). When data do come from a sublinear model, the linearized bound exaggerates the risk as much as it would have in a tough situation (a linear model) instead of only as much as

it would have to for a sublinear model. In simple terms, the linearized bounding procedure always exaggerates the bound considerably regardless of whether it really needs to or not. This also means that the linearized bounding procedure is insensitive to the data because the data really dictate whether the exaggeration is needed or not.

An alternative to the linearized 95% upper confidence limit procedure is bootstrap bounds. An advantage of the bootstrap distribution is that it depends on the observed data and results in bounds that reflect the variability in the experiment. Another advantage is the bootstrap procedure emphasizes the observed shape of the dose-response relationship in the data rather than emphasizing the toughest hypothetical shape. Bootstrap 95% upper bounds may be several orders of magnitude smaller than 95% UCLs based on linearized procedures. The bounds on added risk estimated by the linearized multistage model 95% UCL procedure and by the bootstrap procedure are approximately equal when all lung tumors are considered as the response. However, when only malignant tumors are considered as a response, the 95% UCLs on added risks estimated by the linearized multistage model are 4 to 5 orders of magnitude larger than the bounds by the bootstrap procedure. (pp. 6-8, 6-16 - 6-18)

Response: The potency slopes obtained for the 95% UCL of the linearized multistage models are generally very sensitive to the number of tumors in the lowest dose group but not to higher dose groups. In removing all malignant tumors from the count, as suggested by the commenters, the shape of the overall curve is profoundly changed (commenters' Fig 6-2), but the lowest dose group is unaffected. So the 95% UCL is not greatly affected.

The commenters have made a good case for using the bootstrap approach to determine the upper 95% UCL if the use of only malignant tumors were justified, but it is not. The TSD's analyses exclude squamous cysts but follow the appropriate practice of including benign precursors of malignant tumors in modeling human cancer risk from animal tumor data. Note that a reason for the jagged shape of the commenters' relationship is likely to be the exclusion of adenomas which may soon progress to adenocarcinomas.

34. Comment summary: The lack of a weight-of-evidence evaluation of animal studies causes the TSD to exaggerate the animal-based risk projections. Cal/EPA used the study that had the largest proportion of responses to estimate the upper confidence limits on cancer potency. Overlooking all the available information in favor of the one data set that results in the largest upper confidence limit on cancer potency is a common practice in regulatory agencies. Including the evidence from all the available animal studies should improve the quality of estimates. Using a weight-of-evidence approach would allow this in the determination of the distribution of animal-based added risks. (pp. 6-8, 6-18)

Response: Actually, the animal study with the highest risk based on upper confidence limits is that from Brightwell et al. (1989). The data from Nikula et al. (1995) also indicate a slightly greater risk than that from Mauderly et al. (1987). The Mauderly et al. study was selected due to its superior reporting and study design. A comparison of 5 animal bioassays is now given in Chapter 7 of the TSD.

35. Comment summary: Average lung burden should be emphasized over environmental concentration as the dose scale for modeling. Average lung burden accounts for all the processes that occur between the environmental concentration and the actual amount of the agent that reaches the target organ. That is, lung burden is a measure of dose that is more biologi6ally relevant to the causation of cancer than the environmental concentration. (p. 6-19)

Response: OEHHA staff agree that lung burden is a useful measurement of dose for calculating cancer risk for diesel. The risk estimates from animal data include estimates using lung burden as the dose metric. The analogous calculation with diesel air concentration is given for comparison.

36..Comment summary: A comprehensive risk assessment should estimate the risk to populations as well as subpopulations. Making a decision based on estimated risks for the most sensitive subpopulation does not guarantee optimal utilization of health protection resources and hence does not guarantee maximal public health protection. Furthermore, portraying all of the individuals in a population or a subpopulation as having the same exposure or dose-response characteristic does not reasonably describe the distribution of risks in the population or subpopulation caused by variability from individual to individual. (p. 6-19)

Response: It is difficult for us to describe the distribution of risks caused by variability from individual to individual, as the comment suggests, because we do not possess extensive exposure or health effect data for individuals. The reference concentration (RfC) presented in the TSD is an estimate which is intended to protect sensitive individuals as well as the average person. Consideration of sensitive individuals for the setting of public health standards has many years of precedent in California and the nation. The calculation of the RfC includes an uncertainty factor to account for individual variation in response.

37. Comment summary: Cal/EPA has selected the Garshick et al. (1988) study to estimate lung cancer risk due to diesel exhaust. Considering that smoking is estimated to be responsible for over 90% of lung cancer cases, a quantitative risk assessment of lung cancer based on a study in which the smoking status of the study population is unknown has little or no validity. (p. 6-33)

Response: The epidemiological analyses use multiplicative models to calculate relative risk. The relative risk for diesel exhaust in such models is independent of any effect beside diesel exhaust unless the diesel exhaust turns out to interact with another effect. The Garshick et al. (1987a) case-control study, on a closely related population, investigated the interaction between the effect of smoking and the effect of diesel exhaust and found none. Hence, the ultimate multiplication of relative unit risk by the lung cancer risk in the target population yields the appropriate adjustment of smoking or other effects to fit the target population.

38. Comment summary: With regard to Garshick et al. (1988), Cal/EPA has made several arbitrary decisions regarding exposure levels. For example, it is assumed that the level of diesel exposure for shopworkers increased 15 times from 1945-1960. The TSD notes that because of the greater degree of "smokiness" of earlier engines, an exposure factor of 2 times the average level of 1983 was used for other workers. Although Cal/EPA has gone to great lengths to defend these assumptions, it is noteworthy that the TSD authors have ignored exhaust emissions in the

shops prior to dieselization. Steam locomotives burned primarily coal and would have had significant emissions of respirable particles. The difference in emissions between steam and diesel locomotives should be examined before making any conclusions regarding exposure levels during the various time periods. (p. 6-33)

Response: The level of diesel exposure factor of 15 for shop workers was not arbitrary. It was taken from measurements of a surrogate, as described in Section 7.3 of the 1994 draft TSD. The level of 2 for exposure factor for other workers was an estimate to represent the greater smokiness of the earlier period, and the precise level is subject to some uncertainty, such as assigning an integer value. These numbers are clearly uncertain, but they are unlikely to be more than 2-fold higher or lower than the true values.

In regard to railroad exposures prior to the completion of dieselization, exposures which were primarily to the products of combustion of coal in the steam locomotives, Kaplan et al. (1959) calculated a standardized mortality ratio of 0.87 (90% CI: 0.68-1.11) for a large U.S. railroad during the years 1953-58. This result for the years during which dieselization was nearing completion would have been heavily influenced by the prior exposures. This observation therefore suggests that any lung cancer from those prior exposures was a small effect in comparison to that found in the later North American railroad studies with relative risks near 1.5. The particle size of the prior emissions would be expected to be much larger than that of diesel exhaust, even in its typical agglomerated form. More specific information, for example from the industrial hygiene files of the railroad companies, might permit further investigation of this point.

39. Comment summary: Considering the readily apparent weaknesses and inconsistencies of the Garshick et al. (1988) study, it is surprising that Cal/EPA has based the entire human risk assessment on this data. Because the study lacks too much information regarding exposures (to diesel exhaust, cigarette smoke, asbestos, and potentially other substances), it is not an appropriate study on which to base risk calculations. Others have arrived at a similar conclusion regarding the railroad studies. Because of the inherent weaknesses of the study, the various assumptions used by Cal/EPA in establishing a cancer slope factor from the Garshick study are meaningless. To comment on them further would be pointless. (p. 6-33)

Response: Cal/EPA has not based the entire risk assessment on a single study. The health assessment evaluates all the relevant toxicologic and epidemiologic information available. In the 1994 draft TSD, a best estimate of unit risk was proposed based on the Garshick et al. (1988) cohort study. Because of uncertainties in the quantitative risk assessment based on the Garshick et al. (1988) study, the revised TSD investigates a number of aspects of using that study in quantitative risk assessment. These include reanalysis of the individual data for the workers by a number of analyses to better characterize the range of risk due to a variety of models and assumptions for that study (see Chapter 7 and Appendix E of Part B). The revised TSD also includes an analysis based on the Garshick et al. (1987a) case-control study. The result is the finding that, in spite of some limitations of the full set of data, some uncertainties in exposure, some potential for confounding and some other uncertainties, the study is suitable for use as the basis of a quantitative risk assessment.

40. Comment summary: Several comments in the conclusion section of the quantitative cancer risk assessment (Section 7.5 of Part B) should be clarified. There, the TSD states that "The use of a human study as the basis for calculations of unit risk is consistent with identifying diesel exhaust as a human carcinogen in view of the large number of positive human studies." Yet there is not a large number of positive human studies. Because of limitations and methodological flaws, one cannot reasonably conclude that any of the cited studies has shown a positive relationship of human health effects to lung cancer. The primary problem with using the human study is the uncertainty in estimating exposures. The most significant uncertain exposure appears to be cigarettes and not diesel exhaust.

The statement that the table evaluating the strengths and weaknesses of the animal and human studies "appears to give the use of human data a slight edge" is surprising considering that the extent of exposure in the human study was never measured and there was undoubtedly an extremely high prevalence of smoking among the human subjects. (pp. 6-33 - 6-34)

Response: Regarding whether diesel exhaust is a human carcinogen, the TSD thoroughly evaluates the increased relative risks of lung cancer observed in the epidemiologic studies and their association with diesel exhaust exposure. The TSD notes that a principal source of uncertainty in the quantitative risk assessment based upon the epidemiological data is the limited exposure history. Smoking as a potential confounder is discussed in the revised TSD in Section 7.3 and Appendix D of Part B. (See also-response to Comment 39.)

The statement giving the human data a slight edge does take into account the uncertainties in the exposure, which did have a measured baseline in U.S. railroad workers. There was a high prevalence of smoking among the human subjects.

41. Comment summary: In Part B, Table 7-10 appears to be misreferenced as Table 7-8 in Section 7.5. (p. 6-34)

Response: This has been corrected (this table is now Table 7-12).

42. Comment summary: The commenter strongly disagrees with the TSD's conclusions that there is sufficient evidence to designate diesel exhaust as a human carcinogen and that there is a zero threshold level for carcinogenicity. These conclusions have not been adequately established and should not be used in the evaluation of diesel exhaust as a "toxic air contaminant." (p. 6-34)

Response: With regard to threshold, the TSD does not affirmatively claim that there is no threshold for diesel exhaust carcinogenicity. The document does note, however, that the mechanism of action by which diesel exhaust induces lung tumors in rats is not established. Moreover, the document does not specify a mechanism for potential carcinogenicity in humans. Regarding whether diesel exhaust is a human carcinogen, the TSD thoroughly evaluates the increased relative risks of lung cancer observed in the epidemiologic studies and their association with diesel exhaust exposure. The term "sufficient" is not used in evaluating the evidence regarding diesel exhaust and cancer in humans.

Joint Comments
(of 50 organizations)

1. Comment summary: Taken as a whole, available scientific evidence does not support listing of diesel exhaust as a toxic air contaminant (TAC) 'to the extent proposed in the preliminary ARB/OEHHA documents. (Comments dated October 14, 1994, p. 3)

Response: After considering the available scientific evidence, OEHHA staff found that diesel exhaust meets the definition of a toxic air contaminant. The analysis of the data includes both cancer and noncancer health effects information from both human and animal studies. The available data do not allow the identification of a threshold exposure level below which no significant adverse health effects are anticipated.

2. Comment summary: ARB and OEHHA should carefully consider the broad impact of a decision to list diesel exhaust as a TAC. The TAC Identification process should ensure comprehensive evaluation of available data and any associated uncertainties. The process also should include application of alternative risk assessment methodologies to quantify the effects of highly conservative, policy-driven assumptions incorporated into state-approved risk assessment methodologies. (p. 4)

Response: OEHHA staff have endeavored to prepare a risk assessment document based on comprehensive evaluation of the available data and associated uncertainties. Part B of the TSD was prepared with careful attention to the assumptions that are necessary in risk assessment, and several different risk assessment methodologies are detailed there. The document now presents a relatively broad range of risk estimates which fairly apprises risk managers of the uncertainties involved in the estimated values. A formal quantitative uncertainty analysis is beyond the scope of the resources available to OEHHA.

3. Comment summary: The TAC identification process must provide adequate time for full consideration of available data. In addition to the issues discussed in the commenters' submittal, there are many more issues which deserve further analysis. These issues may include: assessing the validity of using rat data as a surrogate for human exposure; assessing the influence of a "threshold effect" on carcinogenesis and defining that threshold; and conducting a follow-up study of the Garshick cohort, with emphasis on controlling for confounding factors (e.g., smoking, diet). Analysis of these and other issues will require a longer-term, cooperative commitment by ARB, OEHHA and industry. In addition, both the Part A & B documents contain numerous requests for additional information, recommendations, or clarification to address recognized uncertainties. The proposed process timeframe should allow for adequate analysis of these uncertainties. (pp. 4-5)

Response: The Toxic Air Contaminant program provides for an open public process with adequate time for reasonable consideration of the available data and associated uncertainties. With respect to diesel exhaust, an extensive effort has been made to acquire public and scientific input. Diesel exhaust entered the TAC program in 1989. ARB sponsored a conference on diesel exhaust risk assessment in March 1990. The first draft TSD was released to the public on June

17, 1994, and was the subject of a public comment period. A public workshop on the document was held on September 14, 1994. Documents by U.S. EPA and Health Effects Institute were released that year and have been considered in our development of the current (second) draft. OEHHA co-sponsored a scientific workshop with NIOSH, W.H.O., U.S. EPA and ARB on the human data in early 1996. The current draft TSD will be subject to further public review and input. A draft will also be reviewed by the Scientific Review Panel (SRP) on Toxic Air Contaminants. Only after the SRP approves the TSD and prepares written findings will the ARB decide whether to list diesel exhaust as a TAC.

The current state of the issues which the comment suggests deserve further analysis is reflected in the TSD. Many of the raised issues involve the use of the animal cancer bioassay data in the risk assessment. OEHHA acknowledges in the TSD the uncertainties involved in the use of those data and the TSD therefore places greater emphasis on the human data. In general, given the state of the available information, further analysis is not likely to provide much useful resolution. The current draft now includes a meta-analysis which considered sources of potential confounding and provides information regarding the carcinogenicity of diesel exhaust. The results of the meta-analysis were not strongly dependent upon the Garshick cohort study.

4. Comment summary: The TSD's exposure and health risk conclusions must be evaluated for consistency with legislative mandates. SB 1082 of 1993 changed the standard of review by the Scientific Review Panel. Health effects reports are required to be based on "sound scientific knowledge, methods and practices." This is particularly important in view of the fact that the TAC identification process does not prescribe specific criteria to ensure that the evidence cited in support of listing is in fact conclusive. There is sufficient uncertainty in the draft documents to support more thorough exposure and health risk assessment analyses. (p. 5)

Response: OEHHA staff believe that the TSD is based on "sound scientific knowledge, methods and practices." As noted in the comment, however, this standard is for the SRP to apply. The ARB determines whether or not the evidence supports listing a substance as a TAC. The statutory definition of a TAC serves as the Board's criterion, and the Board is aided in its decision by the written findings of the SRP.

5. Comment summary: California's process should complement work in progress at the national level, including a Health Effects Institute report on diesel exhaust health effects, U.S. EPA's Revised Draft Diesel Exhaust Health Risk Assessment and a review of diesel exhaust data by the National Institute for Occupational Safety and Health (NIOSH). The TSD does not make clear the extent to which California intends to evaluate this work and incorporate the findings of these analyses in the diesel exhaust TAC process. 1993 California legislation, (AB 969, Jones, AB 1144, Goldsmith, and SB 1082, Calderon) requires that agencies provide clear justification for promoting regulations that differ from federal requirements and which impose material economic hardship. Given the potentially severe consequences of a different California approach for a toxicity-based diesel exhaust regulation, the California process should proceed in tandem with the federal process and related work by nationally recognized scientific bodies. The World Health Organization is also conducting a review of diesel exhaust toxicity which may provide

additional insight into the possible human health effects associated with low-level diesel exhaust exposures. ARB and OEHHA should evaluate the conclusions of this analysis. (pp. 5-6)

Response: OEHHA staff have worked to ensure that our risk assessment process is based upon sound and objective science and fully considers the HE.I., U.S. EPA, NIOSH and W.H.O. work referenced in the comment. OEHHA reviewed both the U.S. EPA and W.H.O. approaches to the chronic non-cancer health risk assessment for diesel exhaust and concluded that adoption of the U.S. EPA RfC was appropriate. It should be noted that these agencies are not in consensus on all important points with respect to the carcinogenic potential of diesel exhaust. OEHHA has closely considered the varying assessments of these agencies. In fact, OEHHA and AFB co-sponsored a scientific workshop with these other agencies in early 1996 on diesel exhaust risk assessment to explore the bases of the differing interpretations of the epidemiological findings. OEHHA has been involved in on-going discussions with U.S. EPA staff in particular on how to best achieve a reliable characterization of the health risks of diesel exhaust.

AB 969 and AB 1144 amended California's Administrative Procedure Act, which has subsequently been amended again by 1994 legislation, AB 2531 (Gotch; Chapter 1039, Statutes of 1994). ARB will follow the procedures specified in the Act if it promulgates regulations (e.g., a toxic air contaminant listing) based on our TSD. With regard to SB 1082, OEHHA staff believe that the TSD is based on "sound scientific knowledge, methods and practices," as required by that legislation.

6. Comment summary: The TSD should consider the effects of recently promulgated regulations and standards on risk from diesel exhaust exposure. A number of regulations and standards pertaining to diesel fuels and diesel-fueled equipment have been promulgated by state and federal agencies in recent years. The health effects studies referenced in the TSD are primarily based on exhaust from outdated fuel formulations, limited-application fuel formulations and outdated engine technology. (p. 7)

Response: It is likely that the composition of diesel exhaust does vary somewhat with equipment (source) modifications and fuel formulation. Whether these variations importantly impact the risks associated with diesel exhaust cannot be assessed without quantitative speciation of the components of the exhaust at issue and an index of the toxicological concern associated with each of the measured components. Because this information is not available, we have not been able to take into account, in the risk assessment, differences among different types of diesel engines, model years, or fuels. While the Air Resources Board is sponsoring work to speciate the components of current diesel exhaust, there are likely to be a great many constituents of diesel exhaust for which there will be insufficient or no data on which to base an index of toxicological concern.

Part B's unit risk estimates are applied to exposure estimates provided by ARB. The exposure estimates reflect government controls and other innovations that have occurred. The exposure estimates are current.

7. Comment summary: The lung cancers identified in the health effects data are a result of particle accumulation in the lung (overload carcinogenesis) and do not result from low-level diesel exhaust exposures. Adequate consideration of this issue should result in substantially reduced risk estimates. (p. 7)

Response: OEHHA staff have considered the hypothesis that diesel exhaust carcinogenesis is due to particle overload in the lung. As stated in Part B's Chapter 6, the mechanism of action by which diesel exhaust induces lung tumors in rats is not established. The animal data-based risk estimates in the TSD have not been substantially modified. See also response to comment 12 below.

8. Comment summary: Differences between U.S. EPA and OEHHA in estimating health risk are significant and must be reconciled. Last year, U.S. EPA published its "Mobile Source-Related Air Toxics Study" in which it estimated national exposure and health risk from diesel exhaust particulate. The nationally averaged risk due to diesel particulates in the year 1995 is calculated by U.S. EPA to be significantly less than calculated by ARB/OEHHA. This difference is so significant that the reasons for it must be resolved and the two reports made consistent. Risk levels calculated by U.S. EPA are significantly lower than those calculated by ARB/OEHHA. While apparently based on the same health research, the unit risk factor (URF) for diesel particulates used by U.S. EPA is 1.7E-5 $(\mu g/m^3)^{-1}$ while the URF calculated by OEHHA is 3E-4 $(\mu g/m^3)^{-1}$. This difference should be acknowledged as a part of a characterization of the range of uncertainty in estimating exposure to diesel exhaust and the health risk posed by that exposure. This commenter recommends a formal uncertainty analysis. (pp. 9-10)

Response: With the current revisions of Cal/EPA's and U.S. EPA's diesel exhaust risk assessment documents, it is expected that the differences between the agencies will have markedly diminished. Both agencies appear to have followed standard risk assessment practices in characterizing the risks and together their results can be expected to provide a reasonable range of risk estimates. The TSD now presents a range of risk estimates which is anticipated to largely overlap with the U.S. EPA values. While the TSD also has expanded its discussion of uncertainty, a formal uncertainty analysis has not been added to Part B. The benefits to risk managers of such an analysis would probably be small relative to the resources required to conduct the analysis. OEHHA did not have adequate resources to conduct such an analysis for this document.

9. Comment summary: Certain corrections would result in risk estimates at least 100-fold less than given in the TSD. Accounting for additional emissions reductions due to the increased phasing in of motor vehicle control measures, the risk in the year 2000 could be a factor of up to 200 less. These results assume only a factor of 18 reduction in the diesel particulate unit risk factor, to match the value used by U.S. EPA in its Mobile Source-Related Air Toxics Study. However, as discussed elsewhere in these comments, the cancer potency of diesel exhaust may be significantly lower. Accounting for these factors is very important. A risk uncertainty range should be calculated and presented to decision makers, along with an analysis of the broad policy implications within this range.

Response: Part B's unit risk estimates are applied to exposure estimates provided by ARB. The exposure estimates reflect government controls and other innovations that have occurred. The exposure estimates are current.

The TSD is intended to give an assessment of risks at current levels of exposure, and a dose-response assessment that can be applied to current or future exposures, using the mass of diesel exhaust particles as the measure of exposure. If diesel exhaust is listed by regulation as a toxic air contaminant, ARB will certainly take projected (future) exposure levels into account when considering further control measures.

The TSD presents a range of risk estimates and acknowledges uncertainty in the risk assessment process. However, an analysis of the broad policy implications of the risk estimates in the range is not within the scope of Part B.

10. Comment summary: Epidemiological data do not support the conclusion that diesel exhaust is a human carcinogen. The commenters support the conclusion of an American Health Foundation report that, using commonly established criteria for determining causation, available evidence is insufficient to establish diesel exhaust as a human lung carcinogen.

A re-examination by Gradient Corporation of the relative risks for exposed subgroups within the Garshick cohort (see the Comments of the American Mining Congress), underscores this point. The Gradient review indicates that OEHHA's analysis predicts an inverse dose-response relationship. This result invalidates preliminary conclusions of the OEHHA analysis. Moreover, the inverse dose-response relationship indicates that the relative risks reported by Garshick are likely due to effects not related to diesel exhaust exposure. (pp. 14-15)

Response: Our responses to comments of the Engine Manufacturers Association cover the material of the American Health Foundation report. The responses tend to counter the arguments in that report that there is insufficient evidence to establish diesel exhaust as a human lung carcinogen. The TSD does not make a "sufficient evidence" determination, however. Regarding whether diesel exhaust is a human carcinogen, the TSD thoroughly evaluates the increased relative risks of lung cancer observed in the epidemiologic studies and their association with diesel exhaust exposure.

Our responses to the comments of the American Mining Congress cover the material in the Gradient "Critique." The responses counter the Gradient argument and maintain that a positive dose-response relationship for diesel exhaust and lung cancer in the study of Garshick et al. (1988) is a valid finding.

11. Comment summary: No epidemiologic data are appropriate for quantitative risk assessment. Dr. Kenny Crump holds that the Garshick study is not adequate to support a quantitative risk assessment. Dr. Crump cites the following conclusions as a basis for this assertion: (1) a closer look at the two main analyses of Garshick et al. revealed problems that make it highly questionable as to whether the lung cancer trends they described in these analyses were related to diesel exposure at all; (2) despite extensive analyses that involved several different surrogates for

exposure to diesel particulate, several ways of accumulating diesel exposure, separate consideration of several different subcohorts, Dr. Crump was unable to detect a quantitative relationship between diesel exposure and risk of lung cancer in this cohort; and (3) the follow-up of the Garshick et al. cohort was clearly inadequate between 1978 and 1980, the last three years of follow-up. Dr. Crump's overall conclusion is that OEHHA's reliance on the Garshick study is "not scientifically justified".

The commenters understand that Dr. Garshick has directly communicated to OEHHA staff his concern that his railroad worker cohort studies should not be used for quantitative risk assessment. (p. 16)

Response: OEHHA staff have analyzed the 1991 report of the analysis cited in the comment and have had extensive consultations with its principal author, Dr. Crump. Although Dr. Crump has corrected the negative slopes that appeared in the report due to a programming error, he continues to conclude from his further analyses that "the data in the Garshick et al. cohort do not show any convincing evidence of an association between risk of lung cancer and duration of exposure to diesel exhaust or quantitative measures of diesel exhaust" (Crump 1996a). Appendix E of the revised Part B presents new analyses based on the individual data that were the basis for the study of Garshick et al. (1988) and for the analyses of Dr. Crump. The rationale for basing quantitative risk assessment on Garshick's data is developed in Chapter 7. Appendix F is devoted to addressing the issues raised by Dr. Crump.

Since the 1994 publication of the draft TSD, Dr. Garshick has given OEHHA staff helpful suggestions regarding our use of his cohort study (1988) data in quantitative risk assessment. OEHHA staff recently asked Dr. Garshick for assistance in responding to comments such as this one. We asked for his view of the uses to which we have put his data, and we specifically gave him an opportunity to express the opinion, if he held it, that we had misused his data. In response, he reaffirmed his position in a 1994 review letter to OEHHA staff. In that letter, he concluded that "the strength of an assessment of risk depends on the assumptions that go into it.. You have made a number of assumptions that yield values of unit risk somewhat greater than animal studies, but lower than others using human epidemiologic data.. In the end you have to be satisfied with these assumptions. Perhaps it would be better to use a range of potencies as the background for regulating diesel exhaust since considerable assumptions need to be made to use the current human-based data.,' The TSD now emphasizes a range of risk estimates, as advocated by Dr. Garshick.

12. Comment summary: Available evidence suggests that carcinogenicity in the rat is based on threshold effect. A threshold dose exists below which diesel exhaust exposure will not lead to lung tumors in the rat. The OEHHA evidence of "genotoxicity and of quantitative analysis of the cancer bioassay" is based on incomplete evaluation of available data. New evidence shows that, first, the OEHHA assumption of genotoxicity of diesel exhaust inappropriately uses organics removed by industrial solvents as a surrogate of particle action. These conditions do not exist in the living organism and whole diesel particles produce no or minimal mutagenic activity when tested by laboratory assays. Second, the organic fraction on the diesel particulates is not readily released by physiological fluids. Third, long-term animal studies display a clear carcinogenic no-

effect level in animals exposed to relatively high (up to <1.0 mg/m^3) concentrations of diesel exhaust that exceed California's preliminary ambient levels by at least two orders of magnitude. Comments of Joe L. Mauderly support this point, and mention studies supporting the view that the rat's response to diesel exhaust may be a general response to heavy particle loading of the rat lung, and that such data might be of little or no value for predicting human lung cancer risk at lower exposure rates. This alternative mechanism was already proposed in 1986 and has been endorsed by new animal studies since that time.

Currently, the scientific community predominantly believes that the tumors occur whenever lung clearance mechanisms are overburdened by high levels of fine particles (an "overload"), irrespective of their chemical composition. The soot-associated organic compounds do not support the estimation of human lung cancer risk from rat data on the basis of the particle associated organic compounds. The lack of genotoxic mechanism involvement further supports evidence that there is a threshold below which overloading (and possible subsequent lung tumor formation) does not occur. These findings explain formation of diesel-induced lung tumors by non-genotoxic mechanisms, support the existence of a threshold for low-level diesel exposures and should substantially modify OEHHA's preliminary unit risk estimates.

In this regard it should be noted that lung tumor formation due to diesel exhaust exposure is observed only in rats. Mouse data are inconclusive and hamster data do not show lung tumor formation. Some scientists contend that: 1) the carcinogenic-response observed in the rat may be a rat-specific effect, 2) that the rat data does not contribute to the quantitative weight of evidence that a chemical poses a human carcinogenic hazard, and 3) (therefore) the rat data should not be included in dose-response extrapolations for the estimation of human carcinogenic risk. (pp. 17-18).

Response: See responses to Comment 7 above and the comments of Joe L. Mauderly. As stated in Chapter 6 of the TSD's Part B, the mechanism of action by which diesel exhaust induces lung tumors in rats is not established. The available data do not rule out a threshold. Note that the possibility that genotoxicity due to the PAH and nitroPAH content of diesel exhaust plays a role in the induction of lung tumors in rats at lower levels of diesel exhaust cannot be excluded. This mechanism would probably be relevant to human cancer risk, and would not be expected to have a threshold of action. Chapter 5 of Part B describes extraction under physiological conditions of mutagens from diesel exhaust, as well as increased lymphocyte DNA adducts in humans occupationally exposed to diesel exhaust. In addition, The proposed "overload" mechanism includes chronic inflammation and associated production of inflammatory cytokines and increased cell proliferation. As noted in a recent paper by Gaylor and Zheng (1996), (1) a threshold dose is questionable if a carcinogen acts via a cell receptor, (2) even a nongenotoxic carcinogen that increases the cell proliferation rate by augmenting an endogenous mechanism is not likely to have a threshold dose, and (3) dose response curves for cell proliferation and tumor incidence do not necessarily mimic each other.

The statement in Chapter 1 regarding "genotoxicity" and "the cancer bioassay" has been grammatically improved and modified slightly for the current draft. It now reads, "The in vitro and in vivo genotoxicity of diesel exhaust suggests that a non-threshold mechanism for

carcinogenesis may be involved. The Moolgavkar quantitative analyses of the rat cancer bioassay did not suggest there was a threshold for the carcinogenicity of diesel exhaust in the rat."

13. Comment summary: Review of epidemiological data on carbon black workers suggests that extrapolation of human risk from animal data is not appropriate. The absence of lung cancers in occupationally exposed carbon black and coal workers must be better quantified before one can draw a conclusion concerning the health effects of diesel exhaust. The same animal model that showed high concentrations of inhaled diesel particulate to be carcinogenic in rats also has shown that rats inhaling airborne carbon black (with no associated organics) also develop lung tumors at equivalent (or even lower) exposure concentrations. The rat data suggest that carbon black and diesel exhaust are of equivalent carcinogenicity and would predict similar cancer potency factors. The validity of the rat-human extrapolation for diesel exhaust can be tested by examining whether the tumorigenicity of carbon black in rats is concordant with lung cancers in workers exposed to carbon black. A 1981 report on carbon black epidemiology summarizes data on carbon black workers and contains data on carbon black exposure levels. The high lung cancer rates predicted for carbon black workers by the animal data are not substantiated by industry experience, which raises serious doubts concerning the validity of the rat-human extrapolation for diesel exhaust. (pp. 18-19)

Response: In response to this and related comments concerning carbon black and diesel exhaust, Chapter 7 of Part B now discusses the question of rat-to-human extrapolation that is raised by the apparent differences in the comparative carcinogenicity of the two different substances in the two species. Also in response, the new Appendix C of Part B summarizes the limited literature on occupational cancer epidemiology of carbon black exposure, adding a new case-control study which found some increase in risk for all lung cancers and a significantly greater risk for one histological type of lung cancer in carbon black workers with a relatively high exposure. This summary refers to the 1981 report mentioned in the comment. Appendix C also provides alternative calculations for comparing the lung cancer deaths observed in the carbon black workers of Robertson and Ingalls (1980) to predictions from the Garshick et al. (1988) cohort study of the effect of diesel exhaust on lung cancer in railroad workers. These calculations show that for many reasonable assumptions the predictions for diesel exhaust do not differ significantly from the observed lung cancer deaths among the carbon black workers and for other reasonable assumptions the predictions do differ significantly from the observations. Thus the comparison of the human results for carbon black and diesel exhaust does not appear to be in contradiction to the comparison of the rat results.

The possibility cannot be excluded that genotoxicity due to the PAH and nitroPAH content of diesel exhaust plays a role in the induction of lung tumors in rats. This mechanism would probably be relevant to human cancer risk, and would not be expected to have a threshold of action. Chapter 3 of Part B discusses bioavailability and metabolic activation of particle-associated organics, and Chapter 5 describes extraction under physiological conditions of mutagens from diesel exhaust. Chapter 5 also cites findings of increased lymphocyte DNA adducts in humans occupationally exposed to diesel exhaust, and the occurrence of a specific DNA adduct in diesel exhaust-exposed rats which was not observed in rats exposed to carbon black. This is a fundamental difference between diesel exhaust and carbon black exposures, and

indicates that comparing rat and human responses to carbon black exposure may not be completely applicable to determining if rat lung tumor response to diesel exhaust exposure accurately models human cancer risk. Thus it is not clear that the validity of rat-to-human extrapolation for diesel exhaust can be tested by examining whether a similar rat-to-human extrapolation for carbon black is concordant with lung cancers in workers exposed to carbon black.

The situation regarding the assertion of lack of elevation of lung cancer rates in coal worker studies is different. Coal dust has very different characteristics, especially in particle size and shape (for example, specific surface), compared to either diesel exhaust or carbon black. So it should not be expected to have the equivalent toxicity. The generally large particle size suggests a more central deposition pattern in the lung. The different shape may suggest different carcinogenic potential, especially if surface area is important. Thus a finding of no detectable carcinogenic effect of coal dust appears unlikely to bear on the issue of carcinogenicity of diesel exhaust.

14. Comment summary: Species differences are not adequately evaluated in extrapolating risk from rats to humans. The rat may be unique in its lung-tumor response to diesel exhaust exposure. Chronic exposure of hamsters to high concentrations of diesel exhaust does not produce lung tumors. Results in mice are equivocal. Moreover, recently conducted studies have been unable to reproduce positive findings reported earlier. Several lines of evidence suggest that a unique and species-specific biological response occurs in the rat and thus the evidence may be critical when extrapolating from rat models of particle-induced lung tumors to human exposures.

The rat lung tumor findings are similar to those of male rat kidney tumor studies in that they do not contribute to the quantitative weight of evidence that a chemical poses a human carcinogenic hazard. Therefore, such tumors should not be included in dose-response extrapolations of human carcinogenic risk. (pp. 19-20)

.Response: OEHHA staff have considered the hypothesis that the rat is unique in its lung tumor response to diesel exhaust, and have not substantially modified the animal data-based risk estimates in the TSD. As stated in Chapter 6 of Part B, the mechanism of action by which diesel exhaust induces lung tumors in rats is not established. The available data do not rule out a threshold. Note that the possibility that genotoxicity due to the PAH and nitroPAH content of diesel exhaust plays a role in the induction of lung tumors in rats at lower levels of diesel exhaust cannot be excluded. This mechanism would probably be relevant to human cancer risk, and would not be expected to have a threshold of action. Chapter 5 of Part B describes extraction under physiological conditions of mutagens from diesel exhaust, as well as increased lymphocyte DNA adducts in humans occupationally exposed to diesel exhaust. In addition, The proposed "overload" mechanism includes chronic inflammation and associated production of inflammatory cytokines and increased cell proliferation. As noted in a recent paper by Gaylor and Zheng (1996), (1) a threshold dose is questionable if a carcinogen acts via a cell receptor, (2) even a nongenotoxic carcinogen that increases the cell proliferation rate by augmenting an endogenous mechanism is not likely to have a threshold dose, and (3) dose response curves for cell proliferation and tumor incidence do not necessarily mimic each other.

The TSD (see Chapter 7 of Part B) is clear about the uncertainties, including species differences, evaluated in extrapolating risk from rats to humans. The document's discussion of species differences is more than adequate, given the. limited nature of the available data. Mechanisms of carcinogenesis and sensitivity to carcinogens may differ among species. The assumption that humans are at least as sensitive to a carcinogen as the most sensitive animal species tested (in this case, the rat) is health protective. The rat lung tumor data have not been shown to be mechanistically irrelevant to human cancer risk from diesel exhaust inhalation and, with uncertainties associated with the use of these data acknowledged, provide information useful in the characterization of the potential magnitude of the human cancer risk associated with diesel exhaust exposure.

Hamsters treated with diethy1nitrosamine or benzo[a]pyrene (but not exposed to diesel exhaust) unexpectedly showed only low incidences of respiratory tract tumors (Heinrich et al., 1986). Low pulmonary sensitivity to genotoxic carcinogens could potentially account for the lack of carcinogenic response to diesel exhaust in hamsters. Although investigators have conducted three studies of diesel exhaust inhalation and lung cancer in hamsters (these are described in the TSD), OEHHA staff do not generally consider the hamster to be a useful model for qualitative or quantitative risk assessment of potential human lung carcinogens. In reporting their negative findings with diesel exhaust, Heinrich et al. (1986) pointed out that "contrary to the rat," hamsters have "failed to develop lung tumors ... after inhalation of high concentrations of pure BaP (benzo(a)pyrene] or even cigarette smoke, a well known human carcinogen." Ten years later, the International Agency for Research on Cancer (1996) specifically addressed the relative strengths and weaknesses of the hamster model for different tumor types. IARC, too, noted that there have been no reports of lung tumor development in hamsters due to inhalation of benzo(a)pyrene or cigarette smoke. IARC stated that even with radionuclides it is difficult to induce lung tumors in hamsters, except with intratracheal instillation of polonium-210. Nickel and silica were both negative in hamsters upon inhalation or instillation. Instillations of glass fibers and asbestos have yielded mixed results. The insensitivity of the model indicates that hamster data should not be considered valid predictors of human lung cancer risk.

The studies with male rat kidney tumors (induced by unleaded gasoline) included mechanistic information which indicated specifically and sufficiently that a mechanism was involved which was not present in humans. As stated in Chapter 6, the mechanism of action by which diesel exhaust induces lung tumors in rats is not established. However, for reasons related to uncertainties inherent in interspecies extrapolation, OEHHA gives greater emphasis to the risk estimates based upon the human epidemiological findings.

15. Comment summary: Inclusion of benign squamous cysts among malignant lung tumors will lead to overstated unit risk and is not scientifically justified. Lung pathologists appear to be reaching a consensus that squamous cysts in rat lungs are a benign lesion that should not be included in the lung tumor category. Hence, diesel exhaust risk estimates that include squamous cysts in the count of total rat tumors will overstate potential risk. Recalculated cancer potency factors accounting for removal of squamous cysts from the lung tumor category show that OEHHA's predictions may be overstated by a factor of 1.3. The results emphasize the necessity for caution when extrapolating human health effects from animal data. (p. 20)

Response: A definitive consensus on whether squamous cysts are precursors to squamous cell carcinoma has not been reached (Kittel et al., 1993). The presence of the cysts is treatment-related and there is controversy among scientists on this point. Nevertheless, the risk analysis in the revised document has been done without inclusion of the squamous cysts.

16. Comment summary: The anatomical location and distribution of tumor types that were observed in the rat lungs are not typical of the lung cancers observed in humans. Moreover, the duration of exposure in all positive experiments exceeded that recommended by the National Toxicology Program, and since the tumors appeared predominantly in the oldest rats, one cannot make a direct comparison between all positive predictions and results from other NTP assay systems. (p. 20)

Response: It is generally accepted that tumor site concordance between humans and a bioassay species is not expected in many cases when extrapolating human cancer risk from animal tumor data. With regard to NTP study design, current NTP inhalation bioassays use an approximately 2-year exposure duration. NTP uses the 2-year protocol as a way to standardize the results of its bioassays for internal consistency. Many studies conducted outside NTP use protocols that vary in length, yet these studies still yield useful information. The longer the duration of the exposure and experiment, the more information is gleaned about chronic long-term health effects. For these reasons, one need not discard data from a well-conducted study simply because the duration does not conform to a specific standard. NTP has not done a cancer bioassay on diesel exhaust by any route of administration, therefore it would not be possible to make a direct comparison between the Mauderly et al. (and other positive) studies and results from NTP.

17. Comment summary: Preliminary quantitative risk estimates should not be used to characterize potential human health risk. Based on certain comments of the Western States Petroleum Association (prepared by Tony Cox), these commenters believe that the preliminary risk estimates contain several important shortcomings. Additional information should be considered and more realistic quantifications of uncertainties about risks should be prepared in a revised risk assessment. (pp. 20-22)

Response: The TSD is preliminary in the sense that it is a draft. However, it is intended to be a useful characterization of potential human health risks. OEHHA staff considered the comments of the Western States Petroleum Association, and have addressed the perceived shortcomings (see responses elsewhere in this Part C). The current draft of the TSD reflects consideration of additional information and includes additional quantification of uncertainty. However, a formal uncertainty analysis is beyond the scope of the document.

Comments of Joe L. Mauderly of the Inhalation Toxicology Research Institute (ITRI), Lovelace Biomedical and Environmental Research Institute, Inc. (ITRI is operated under contract for the U.S. Dept. of Energy)

1. Comment summary: The commenter agrees with the general approach of estimating the lung cancer risk from inhaled diesel exhaust from the epidemiological data, rather than from the animal bioassay data. The commenter believes that the unit risk value selected is reasonable, based on our present knowledge. The commenter's confidence in the value is bolstered by the fact that this estimate is within the range of many others calculated using different methods over the past decade. The document (Part B of the TSD) will undoubtedly come under strong criticism because of the considerable uncertainty of the human exposure estimate.

The commenter supports the general approach taken to review existing information and develop a summary risk assessment. Three particular features make this a good effort. First, although a number of studies are reviewed, the final assessment relies on the two studies, one of animals and one of humans, that are considered to be the most useful. In the commenter's view, this is a better approach than attempting to integrate information from a number of animal or human studies. Second, multiple methods are used to derive unit risk estimates from both the animal and human data. This results in the demonstration of a range of outcomes, and lends credibility to the selection made for the best estimate of risk. Third, although risk estimates are derived from both the animal and human data, the Office elected to use an estimate derived from the human data on the basis of the "lesser of evils" regarding uncertainty. In the face of our growing understanding of the rat's lung tumor response to heavy particle exposures, and our growing uncertainty about the relevance of that response to human lung cancer risk, the commenter believes that the choice to use the human data was the correct one. (Letter, dated September 2, 1994, p. 1, and comments, dated September 1, 1994, pp. 1-2)

Response: Comment noted.

2. Comment summary: The accuracy of the selected unit risk value can only be considered very uncertain. The human exposure estimate is the document's greatest weakness, because the exposures cannot be known with a high level of certainty. It can be expected that the approach taken to estimate historic human exposures will incur considerable criticism. The document should make mention of the USEPA-sponsored analysis of the railroad worker data performed by Clement International. The Clement report largely served to turn the USEPA from relying on the human data. (Letter, p. 1; comments, p. 1)

Response: The historic exposure estimates mentioned in the comment have indeed been criticized. OEHHA staff have analyzed the Clement report cited in the comment and have had extensive consultations with its principal author, Dr. Crump. Although Dr. Crump has corrected the negative slopes that appeared in the report due to a programming error, he continues to conclude from his further analyses that "the data in the Garshick et al. cohort do not show any convincing evidence of an association between risk of lung cancer and duration of exposure to diesel exhaust or quantitative measures of diesel exhaust" (Crump 1996a). Appendix E of the revised Part B presents new analyses based on the individual data that were the basis for the

study of Garshick et al. (1988) and for the analyses of Dr. Crump. The rationale for basing quantitative risk assessment on Garshick's data is developed in Chapter 7. The issues are further discussed in Appendix F of the current draft of the TSD's Part B.

3. Comment summary: The commenter finds the inclusion of rat squamous cysts as "tumors" inexcusable. The inclusion of the rat lung lesion known as “squamous cyst” together with lung neoplasms as "tumors" is not acceptable today in the U.S. This has been an issue of great debate, but U.S. pathologists generally agree on this issue. This debate and the conclusion, that these lesions are not "tumors" as such, are acknowledged in the document. However, the document continues to include this lesion in the risk estimate. The document acknowledges that their inclusion makes an approximately 30% difference in the outcome; thus, it would seem reasonable to exclude them. The document appears to violate its own stated principle in including them. (Letter, p. 1; comments, p. 2)

Response: In response to this and similar comments, we have removed squamous cysts from the quantitative risk analysis using the tat tumor data set (see Table 7.4).

4. Comment summary: The commenter believes that the terms "soot," "particulate" and "elemental carbon" are used sloppily throughout the risk assessment. There is not sufficient definition that the reader can be certain just what the dose term is in any given section. It is not clear in some sections whether the entire soot particle or just the carbon core (without extractable organics) is being described. This issue is particularly confusing in the description of the risk estimate derived from the rat data. Taking present uncertainties into account, the commenter believes that using the mass of the total soot particle is the best approach to use throughout the document. (Letter, p. 1; comments, p. 2)

Response: The term "soot" refers to diesel particulates, whereas "particulate" refers generically to insoluble particles, including diesel. "Elemental carbon" describes the core material of the particles. To avoid confusion, the term "soot" has been replaced with "diesel particulate matter" and like terms in Chapter 7 of the revised document.

5. Comment summary: It is not clear how the exposure of rats for only a portion of their life span is handled in calculating lifetime unit risks.(Letter, p. 1)

Response: The adjustment for continuity of exposure is linear and is given under the footnote for superscript d in Table 7.2 of the 1994 document. The rats were exposed for more than 2 years, which is longer than the typical default lifespan of a rat. The fact that exposures began at 17 weeks of age is factored into the time-to-tumor Weibull multistage model.

6. Comment summary: The document fails to portray any parameter of risk other than the upper bound of the 95% confidence interval. While the use of this value may be mandated by California law, it does not give a good view of the level of uncertainty associated with the estimate. An expression of the central tendency of risk and the upper and lower bounds of the 95% confidence interval would be more informative to the public and lawmakers alike. (Comments, p. 2)

Response: The TSD's risk assessment provides maximum likelihood estimates (MLEs) as well as 95% upper confidence limits (UCLs). UCLs are generally less variable than MLEs. UCLs are used specifically to account for uncertainty in potency estimation. Lower confidence limits and expectation values from probability distributions can provide indications of the magnitude of uncertainty associated with central tendency estimates. Nevertheless, risk managers employing scientifically accepted practices generally focus on UCLs. The TSD does present lower bound as well as upper bound values of relative risks from epidemiologic studies

7. Comment summary: Regarding paragraph 1 of Part B's Section 1.4: A carbon core of 30% to 80% of the mass overstates the typical range of extractable mass fraction. A range of 60% to 90% would seem more typical of today's emissions. (Comments, p. 2)

Response: The comment does not provide a citation or rationale to indicate why a range of 60% to 90% is more typical of today's emissions. OEHHA staff will defer to Air Resources Board staff on the measurement of attributes of current diesel emissions.

8. Comment summary: Regarding paragraph 1 of Part B's Section 1.4: The meaning of the statement that "elemental carbon ... is somewhat predictable in the lung" is not clear. (Comments, p. 2)

Response: This statement has been removed from the document.

9. Comment summary: Regarding paragraph 4 of Section 1.4.2: The experimental results indicate that the cell proliferation rate is not "linear with dose," if "dose" is taken to be exposure concentration, or concentration x time. Is "dose" in this statement to be taken as lung burden per unit of surface area? (Comments, p. 2)

Response: The term, "dose" in this statement, refers to either lung burden per unit of surface area or air concentration of diesel exhaust.

10. Comment summary: How can the quantitative analysis of bioassay results suggest anything other than a no-threshold effect when no-threshold mathematical models are used? Taken in aggregate, the rat data from several studies of diesel exhaust and other particles strongly suggest a threshold for the cancer response. The mechanisms for this threshold include the accumulation of sufficient lung particle burden to develop a progressive pneumoconiosis accompanied by continued epithelial proliferation which, in turn, only occurs when the particle clearance pathways are overcome by the deposition rate. This commenter believes that the weight of evidence points strongly toward a threshold effect in rats. (Comments, p. 3)

Response: The Moolgavkar model used in Section 7.2.2 of the 1994 TSD does allow for a threshold; the computed threshold term was zero. Although the incidence data for the rat does rise steeply for higher exposures, that fact does not necessarily imply a threshold, let alone quantify a reliable value for a threshold, as would be required for use in quantitative risk assessment. It is becoming clear from recent research that diesel particles behave not simply as inert particles but also have other specific toxicologic effects on the lung and upper airways. For

example, a significant amount of recent human and experimental animal evidence suggests that diesel particles are significantly more effective in inducing immunologically-based allergic and inflammatory responses than activated charcoal particles of similar dimension (see Chapter 4 of Part B).

As stated in Part B's Chapter 6, the mechanism of action by which diesel exhaust induces lung tumors in rats is not established. The proposed mechanism mentioned in the comment is discussed in greater detail in the current version of the TSD. However, the possibility that genotoxicity due to the PAH and nitroPAH content of diesel exhaust plays a role in the induction of lung tumors in rats at lower levels of diesel exhaust cannot be excluded. This mechanism would probably be relevant to human cancer risk, and would not be expected to have a threshold of action; Chapter 5 describes extraction under physiological conditions of mutagens from diesel exhaust, as well as increased lymphocyte DNA adducts in humans occupationally exposed to diesel exhaust.

The proposed overload mechanism includes chronic inflammation and associated production of inflammatory cytokines and increased cell proliferation. As noted in a recent paper by Gaylor and Zheng (1996), (1) a threshold dose is questionable if a carcinogen acts via a cell receptor, (2) even a nongenotoxic carcinogen that increases the cell proliferation rate by augmenting an endogenous mechanism is not likely to have a threshold dose and (3) dose response curves for cell proliferation and tumor incidence do not necessarily mimic each other.

11. Comment summary: Regarding paragraph 4 of Section 1.5: The "choice of model" on line 5 refers to a "model" of what? Does the statement made here imply that the principal uncertainty concerning rat data relates to the choice of rat as a model for human responses, or that it relates to the choice of the mathematical model used to fit the tumor data? The former is the more important uncertainty. (Comments, p. 3)

Response: Here the "model" choice relates to the mathematical model used to fit the rat tumor data. In response to this comment, the statement has been modified to read "dose-response model" instead of just "model."

12. Comment summary: It is not clear what "variable dosing," as used on line 5 of the 5th paragraph on page 1-8, means. (Comments, p. 3)

Response: The point regarding "variable dosing" has been deleted.

13. Comment summary: Regarding the discussion of Takemoto et al. (1986) in paragraph 4 on page 6-3: The term for dissection of animals is "necropsy," not "autopsy." In addition, the document does not specify the sexes of the mice in this study, as it does for other studies. Both male and female mice of both strains were used, and there was no substantive difference in responses between the sexes. (Comments, p. 3)

Response: The TSD has been revised to substitute “necropsy” for "autopsy", and the fact that both male and female mice were used in the study by Takemoto et al. (1986) has been noted.

14. Comment summary: The reader could be misled by the wording of paragraph 4 on page 6-7. While it is true that soot accumulated at all three exposure levels, and that lesions were scaled to the accumulation of soot, no lesions such as those properly described for the higher two levels occurred at the lowest level. The wording implies that disease occurred at all exposure levels, which it did not. (Comments, p. 3)

Response: We agree. The wording of the TSD has been changed in response to this comment.

15. Comment summary: Regarding page 6-7, paragraph 3: The. document seriously errs in stating the number of squamous cysts in the Mauderly et. al. (1987a) study. It is stated that it is not appropriate to include squamous cysts in a cancer risk assessment, and the commenter agrees. Further, on page 6-5, it is stalled that squamous cysts are not used in the present risk assessment. On page 6-7, it is stated that, because "only 3 of the lesions reported as tumors were (benign) squamous cysts, all in the highest dose group," the analysis is "little affected by retaining the authors' terminology". Analysis of Figure 4 in the Mauderly et al. paper clearly shows that there were 11 animals at the high exposure level which had only squamous cysts, not 3. Moreover, there were 2 squamous cysts in the medium exposure group. These data are presented correctly in Table 6.1.c. Overall, eliminating the animals with only squamous cysts results in a change from 29/227 = 12.8% to 18/227 = 7.9%. For the medium level, the change is from 8/221 = 3.6% to 6/221 = 2.7%. This is a substantial change, and ignoring it in the subsequent risk modeling is unacceptable. One cannot acknowledge the issue of the interpretation of the squamous cysts and then ignore it, and particularly not when it makes such a difference as this. (Comments, pp. 2, 3-4)

Response: The revised TSD now omits all squamous cysts from the analysis estimating cancer potency from the rat data of Mauderly et al. (1987). The text in Chapter 6 has been revised to reflect the change.

16. Comment summary: Regarding paragraph 5 on page 6-16: The statement concerning interpretation of the significance of an effect based on whether or not the confidence interval includes a value of 1.0 is only meaningful if you indicate that it is the 95% confidence interval you mean. One could always find some confidence interval that did not include 1.0. (Comments, p. 4)

Response:This text has been deleted.

17. Comment summary: On line 1 of paragraph 5 on page 6-27, "implies" should be “imply”. (Comments, p. 4)

Response: This word has been corrected.

18. Comment summary: In numerous places the name Koizumi is misspelled "Koizumo." The Ishinishi et al. citation on page 6-36 is absent from the main reference list. In other citations, the principal editor of this publication is incorrectly listed as Stöber (e.g., in the second Stöber reference in the main reference list). (Comments, p. 4)

Response: These problems have been fixed in the new version of the TSD: "Koizumo" has been changed to "Koizumi" in the tables, and the references to the Ishinishi et al. publication have been corrected.

19. Comment summary: Some terminology used on pages 7-1 and 7-2 is confusing. First, it is stated that the "second measure is the cumulative exposure to the mass of elemental carbon in the lungs." Then it is stated that the risk assessment focuses on "particulate matter." Then it is stated that light absorption measurements calibrated by soot mass "give the mass of elemental carbon in excised lungs." The first issue is to determine the desired metric for particles. Total particle mass is the best metric in the absence of knowledge of the mechanisms of carcinogenesis in either rats or humans. The second issue is that the light absorption method calibrated by lungs spiked with soot (carbon plus extractable organics) yields data approximating the lung burden of soot, not "elemental carbon." Overall, the terminology and rationale should be tightened up. (Comments, p. 4)

Response: The document should have referred to diesel particles rather than elemental carbon. This has been corrected in the current draft. OEHHA staff apologize for any confusion engendered by the references to elemental carbon in the initial public review draft.

20. Comment summary: Why the squamous cysts were included in calculations on pp. 7-7 and 7-8 is baffling, even if the difference this made is not large. Why is it stated earlier that this would not be done if, in fact, it was? There is no rationale given for not excluding the lesions that would make a stated 30% difference in the estimate. (Comments, p. 4)

Response: The analysis in the revised document has been done without inclusion of the squamous cysts. The revised q_1^* can be found in Table 7-4.

21. Comment summary: Two things are unclear in paragraph 3 on page 7-10. First, while it is true that the average concentration of 3470 µg/m^3 yields a weekly average value of 730 µg/m^3, the rats were not exposed for their lifetime. Exposures began at 17 weeks of age. Using the value of 131.7 weeks for lifespan quoted on page 7-4, the rats were exposed for only 87.1% of their lifespan. How is that taken into account in extrapolating to the presumed 70 year lifespan of humans? Second, it is again not clear at all if you are dealing with the total soot mass or just the elemental carbon mass in these statements. This issue gets completely lost through the explanation of the risk assessment. When the document talks of ambient exposure concentrations for humans, is it talking only of the elemental carbon mass, or the total soot mass? (Comments, pp. 4-5)

Response: The fact that exposures began at 17 weeks of age was entered into the TOX_RISK model for determination of q_1^*. The model adjusts the discontinuous experimental concentration to an average daily equivalent for the lifetime of the animal. No further continuity adjustment for lifespan differences between humans and rats is necessary.

In response to the second question, total particle mass is used in the diesel exposure estimates. OEHHA staff apologize for any confusion over the terms "soot" and "elemental carbon" which

have been replaced in the revised draft by terms such as "diesel exhaust particulate matter." This issue has been clarified in the document both with regard to the exposures in the experiments from which potency factors are derived and with regard to the ambient exposure concentrations to which the potency factors are applied. See response to Comment 19.

22. Comment summary: The figure referred to in the third and fourth paragraphs of Section 7.3.5 is Figure 7-2, not Figure 7-1. (Comments, p. 5)

Response: Section 7.3.5 has been renumbered, retitled, and revised for the revised document. It now appears as Section 7.3.2.2.2. The error has been corrected in the revised document.

23. Comment summary: In the second paragraph on page 7-18, and elsewhere in the risk assessment based on human data, it is presumed that the masses of particulate used are total particulate, not elemental carbon. It is not clear to the reader if this issue is being treated identically for the rat and human estimates. (Comments, p. 5)

Response: The TSD is intended to give an assessment of risks at current levels of exposure, and a dose-response assessment that can be applied to current or future exposures, using the mass of diesel exhaust particles as the measure of exposure. This issue has been clarified in the current draft of the document. OEHHA staff apologize for any confusion engendered by the references to elemental carbon in the initial public review draft.

24. Comment summary: In Figure 7-7 on page 7-43, the term "C burden" is used as a descriptor for several of the unit risks. Does this really mean only the elemental carbon burden, or does it mean the soot burden? This is confused throughout the document, and should be clarified. The two descriptions are not interchangeable. (Comments, p. 5)

Response: The figure has been changed to eliminate reference to "C burden." (The figure is now Figure 7-4.) The issue of carbon versus soot or particle burden has been clarified throughout the document.

25. Comment summary: Regarding the book cited in the Takemoto reference on page R-30: This book had editors in addition to Stöber. They are not listed. This is also true for other of the document's citations of this book. (Comments, p. 5)

Response: The document has been edited to properly cite this work.

Comments of Mercedes Benz

1. Comment summary: This commenter is greatly concerned over the conclusions drawn in Part B of the TSD. The commenter does not believe the document presents current health effects data on diesel exhaust objectively and believes that the conclusions are not supported by the most recent findings on the topic. The commenter's concerns with the document are outlined in the comments summarized below. (Comments dated October 14, 1994, p. 1)

Response: See responses to specific comments below.

2. Comment summary: The carcinogenic effect seen in rats from diesel exhaust exposure has a threshold. OEHHA concluded in the draft document that there is insufficient basis for determining that the carcinogenic effect has a threshold below which no adverse health effects occur; however, this is contrary to the conclusions reached by several well-respected researchers in the area of diesel exhaust studies, some of whom have demonstrated through their own work that the dose-response curve does, in fact, exhibit a threshold. CARB/OEHHA should carefully review the current findings supporting a threshold for the carcinogenic effects attributed to diesel exhaust exposure in rats and address these findings fully in the TSD. (pp. 1-2)

Response: Chapter 6 of the TSD's Part B notes that the mechanism of action by which diesel exhaust induces lung tumors in rats is not established. One proposed mechanism is that exposure to diesel exhaust particulate matter at high concentrations exceeds pulmonary clearance capabilities and causes chronic inflammation which leads to macrophage and/or neutrophil-induced oxidative DNA damage resulting in mutations which are instrumental in the induction of lung tumors, and also to cell proliferation which may be mechanistically important to the promotion of the rat lung tumors. This mechanism may have a exposure threshold of action, suggesting that tumor induction due to this mechanism may have a threshold. Still, this mechanism includes chronic inflammation and associated production of inflammatory cytokines and increased cell proliferation. As noted in a recent paper by Gaylor and Zheng (1996), (1) a threshold dose is questionable if a carcinogen acts via a cell receptor, (2) even a nongenotoxic carcinogen that increases the cell proliferation rate by augmenting an endogenous mechanism is not likely to have a threshold dose, and (3) dose response curves for cell proliferation and tumor incidence do not necessarily mimic each other. There is no consensus among well-respected researchers regarding a threshold level for diesel exhaust-associated carcinogenesis.

It should also be mentioned that the possibility that genotoxicity due to the PAH and nitroPAH content of diesel exhaust plays a role in the induction of lung tumors in rats at lower levels of diesel exhaust cannot be excluded. This mechanism would probably be relevant to human cancer risk, and would not be expected to have a threshold of action; Chapter 5 of the TSD describes extraction under physiological conditions of mutagens from diesel exhaust, as well as increased lymphocyte DNA adducts in humans occupationally exposed to diesel exhaust.

Animal cancer bioassays are very limited in their ability to distinguish between a response threshold and a small added risk from exposure. In general, as here, animal cancer bioassays can not employ enough test animals to demonstrate the existence of a threshold versus some positive incremental risk. Presumably, the commenter is citing other information such as particle overload to argue for a dose response threshold. OEHHA staff have reviewed the current findings claimed to support a threshold for the carcinogenic effects attributed to diesel exhaust exposure in rats; these findings are now addressed more fully in the TSD.

3. Comment summary: The TSD should address the widely-held view that diesel exhaust does not cause genotoxic (mutagenic) effects. Research reports have suggested that the rat's lung tumor response to diesel soot might be a nonspecific effect unrelated to chemical carcinogenesis from the organic fraction. A commenter has written of an epigenetic process, "overload carcinogenesis," as being responsible for this response. Other scientists (one of whom prepared part of a commenter's submission) have found that only laboratory-prepared extracts of diesel particles are mutagenic. This is because the organic fraction adsorbed on the particle surface is readily extractable only in the laboratory using industrial solvents for extraction; the organics are not easily extractable by biological fluids. Many current rat studies point to the conclusion that the effects from diesel exhaust exposure are epigenic [sic] rather than a result of the genotoxicity of diesel exhaust. This commenter believes that if proper consideration were given to these findings, CARB/OEHHA would come to the same conclusion. (p. 3)

Response: The TSD addresses diesel exhaust and genotoxicity. Part B, Chapter 5 has been revised to include studies which indicate that extraction with a phospholipid emulsion resembling a major component of lung surfactant showed substantial mutagenic activity, sometimes greater than that observed after extraction with organic solvents. OEHHA staff have properly considered the available data and have not reached the conclusion that the carcinogenic mechanisms of diesel exhaust operate without themselves affecting the cellular genome.

4. Comment summary: The TSD should explicitly address the view that the mechanism for carcinogenesis in rats from diesel exposure does not occur in humans. Data from recent rat studies have shown this. We must then conclude that the rat studies are poor models for extrapolation to humans. A researcher has stated that "the phenomenon of particle-induced carcinogenesis in rat lungs and its usefulness for estimating human lung cancer risk remain important areas of uncertainty." *A* commenter has concluded that "most scientists having experience in this field are presently inclined to contemplate the lung tumors of rats by diesel exhaust, carbon black and titanium dioxide to be a rat-specific phenomenon of lung overload." Many prominent researchers share this view. It is unreasonable, and unjustifiable, to use rat data for extrapolation to humans knowing that the mechanism of carcinogenesis occurring in the rat will not manifest itself in humans. CARB/OEHHA should review the body of literature on this issue thoroughly and revise the document accordingly. (p. 3)

Response: It has not been established that lung burden overload is the sole mechanism for carcinogenesis in the rat. It is more likely that multiple mechanisms involving genotoxicity, local inflammation, and general particulate effects operate together. Rather than explicitly addressing the view that the mechanism of carcinogenesis in rats from diesel exposure does not occur in

humans (in providing risk estimates based on rat data, the document suggests that the mechanism occurring in rats, or a related mechanism, may also occur in humans), Section 7.2.8 (point 5) of the revised Part B discusses mechanisms that could operate in both rats and humans, and points out that genotoxicity, which may play a role in rat lung tumor formation at lower levels of diesel exhaust, would probably be relevant to human cancer risk. Genotoxic PAH compounds appear to be bioavailable from deposited diesel particles, so non-threshold carcinogenesis mechanisms may be involved. The Moolgavkar model, which does allow for threshold mechanisms to be considered, did not indicate the existence of a threshold for the Mauderly rat data; this also calls into question the notion that lung tumors are due entirely to a nonspecific threshold effect. Estimating human cancer risk from animal data often involves considerable uncertainty, particularly when the mechanisms are not completely understood, as with diesel exhaust. It is possible that the carcinogenic effect in humans is different than in rats. Although as indicated in Chapter 7 human studies are preferred for human risk estimates, with uncertainties acknowledged the animal data have some value, and the TSD provides risk estimates from animal data as well.

S. Comment summary: Although many epidemiologic studies of coal miners have concluded that carbon particles are not carcinogenic in humans, the draft health assessment document for diesel exhaust concludes that the carcinogenic effect of diesel exhaust should be measured against the carbon core of diesel particulate matter. There is persuasive evidence, particularly with regard to coal dust, that indicates carbon particles are not carcinogenic in humans. Coal miners experience particulate lung burdens at levels equivalent to those seen in "overloaded" rat lungs. There is little justification for using the carbon core as the basis for a human quantitative risk assessment of diesel exhaust given the extensive data on coal miners that indicate that the carbon core is not a carcinogenic agent in humans. The commenter has attached a comprehensive review of coal worker health effects from exposure to dusts. (pp. 3-4)

Response: As presented in the review attached to the comments, studies in coal miners have not shown any detectable increase of lung cancer related to exposure to coal dust. This finding does not have any obvious implications for risk assessment of diesel exhaust because the coal dust particles are much larger and of a different character than the diesel exhaust particles. Part B of the TSD has been revised so that it no longer refers to "carbon core" as an exposure measure for diesel exhaust. The mass of diesel exhaust particles has been uniformly adopted as the exposure measure.

6. Comment summary: The TSD should address the probability that the weak association between diesel exhaust exposure in railroad workers and risk of lung cancer found by Garshick in his retrospective cohort study could be confounded due to lack of sufficient information on diet, smoking, and exposure. Most experts agree that Garshick's study addressed many of the weaknesses of earlier epidemiological studies of diesel exhaust exposure, but the failure to account for a number of confounding factors suggests that care must be taken when interpreting the results. Garshick did not control for smoking nor other possible confounding factors such as diet. The study also lacks adequate quantitative exposure data and instead categorizes workers as exposed or unexposed based on job title.

Another commenter has stated that "when a potential confounder is strongly related to the disease, such as smoking, weak associations are more likely to be influenced by failure to control for confounding." The lack of information on smoking and exposure is a major concern and casts doubt on the accuracy of the results and the appropriateness of using the data for quantitative risk assessment. (p. 4)

Response: In Garshick et al. (1988) the authors report, "These results taken in connection with other reported results support the hypotheses that occupational exposure to diesel exhaust results in a small but significantly elevated risk for lung cancer." The design and results of the Garshick et al. (1988) cohort study make it unlikely that smoking could have had much effect on establishing a trend of risk of lung cancer with exposure, as long as smoking and diesel exhaust act independently. Evidence for independence comes from the case-control study of Garshick et al. (1987), which found virtually no interaction between smoking and diesel exhaust in a study group at the same workplace as the cohort study. Independence allows determination of the trend of risk with exposure by simply omitting the unexposed group from the calculation, thereby eliminating the need to characterize differences in the exposed and unexposed populations.

Others, such as Cohen and Higgins (1995), have stated that the elevated relative risk found in the Garshick et al. (1988) cohort study could not be explained by cigarette smoking.

OEHHA staff have seen no evidence that study subjects' diet was different from controls' in any of the studies involving diesel exhaust exposure and lung cancer.

Regarding diesel exhaust exposure estimates, quantitative measures were obtained just after the end of the follow up period for the study and published by Woskie et al. in 1988. The assumption by Garshick et al. is that current exposures by job title were reasonably representative of past exposures for selected job groups. The Woskie et al. data provide sufficient exposure information for use in the diesel exhaust risk assessment.

7. Comment summary: The TSD should address the relevance of relative risks below 2.0. Epidemiologists generally agree that statistically significant but weak associations between exposure and cancer risk tell us very little about causal relationships. A recent article states that "relative risks less than 2.0 are weak and often can be explained by technical bias." Another commenter has pointed out that a certain researcher considered any epidemiological study reporting on environmental lung cancer effects seriously flawed if, at levels of relative risk greater than 1.0 but less than 2.0, it did not attempt to take cigarette smoking into account. It has been noted that leading epidemiologists have questioned a causal relationship between diesel exhaust gas and lung cancer, even in the presence of statistically significant values, as some confounding factors may remain hidden. A published article has noted that "when the odds ratios are 2 to 1 or less, the possibility that the finding is artificial and a consequence of problems in case-control selection or due to the presence of confounders and biases needs to be carefully considered." CARB/OEHHA must address the relevance of weak associations and the validity of using such data for quantitative risk assessment. (pp. 4-5)

Response: Regarding smoking, see response to Comment 6. Regarding relative risks of less than 2.0 as being weak, Monson (1990) classifies relative risks between 1.5 and 3.0 as indicating a moderate association. Also, the meta-analysis in Part B (Appendix D) reaches overall positive conclusions with some relative risks below 1.5.

8. Comment summary: The TSD must address the findings by Dr. Kenny Crump of ICF/Clement and Dr. Chao Chen of the U.S. EPA regarding the validity of the increased risk of cancer found by Garshick based on the railroad worker data. The U.S. EPA contracted with Dr. Crump to prepare a quantitative risk assessment using Garshick's data from the cohort study of railroad workers. Dr. Crump, and his co-author Dr. Chen, conducted over 50 analyses of exposure to diesel exhaust and lung cancer using the Garshick data. Dr. Crump's conclusions were that "none of these analyses demonstrated a pattern that was consistent with an adverse effect of diesel upon lung cancer; in fact, many of them showed a statistically significant negative association."

It has also been noted regarding the Garshick work, that "whatever the cause for the inconsistencies in the cohort study, its credibility as king's evidence for a causal relationship between diesel exhaust gas exposure and lung cancer in spite of the absence of a smoker control is seriously undermined as a result thereof." Dr. Crump's analysis leads to the conclusion that Garshick's results do not support any findings of a statistically significant risk of cancer from diesel exhaust, particularly when considered with other concerns raised about possible confounding factors.

The TSD should acknowledge Dr. Crump's effort to derive a unit risk factor from Dr. Garshick's cohort study and, in particular, address whether this effort was reasonable. The quantitative risk assessment attempted by Dr. Crump was a credible effort. It appears to have identified some very valid inconsistencies and potential problems with the Garshick data that merit consideration by CARB/OEHHA, particularly given that the draft TSD has relied on Dr. Garshick's data for derivation of a unit risk estimate. CARB/OEHHA should do a thorough review of Dr. Crump's work, evaluate its strengths and weaknesses, and address the potential impact of Dr. Crump's results on the quantitative risk assessment in the draft TSD.

The apparent oversight of Dr. Crump's analysis of the Garshick work calls into question CARB's desire to conduct an objective and thorough health risk assessment of diesel exhaust exposure. (pp. 5-6, 7)

Response: The report of Crump et al. (1991) was not included in the 1994 draft TSD because of apparent internal contradictions discussed in Dawson (1995) and because of its not having had a full peer review.. OEHHA staff have analyzed the 1991 report of the analysis cited in the comment and have had extensive consultations with its principal author, Dr. Crump. Although Dr. Crump has corrected the negative slopes that appeared in the report due to a programming error, he continues to conclude from his further analyses that. "the data in the Garshick et al. cohort do not show any convincing evidence of an association between risk of lung cancer and duration of exposure to diesel exhaust or quantitative measures of diesel exhaust" (Crump 1996a). Appendix E of the revised Part B presents new analyses based on the individual data that were the basis for the study of Garshick et al. (1988) and for the analyses of Dr. Crump. The

rationale for basing quantitative risk assessment on Garshick's data is developed in Chapter 7. Appendix F is devoted to addressing the issues raised by Dr. Crump.

In regard to smoking in Garshick et al. (1988), the study was not directly controlled. However, an important argument against confounding due to smoking, undoubtedly the most potent source of possible confounding, is that the study relied on auxiliary information about railroad workers at that time from the Garshick et al. (1987a) case-control study. The case-control study found that smoking adjustment had a negligible effect on risks attributed to diesel exhaust. So the same should hold for the cohort study, the design of which should minimize any smoking effect but cannot preclude an effect.

9. Comment summary: The TSD should address the fact that recent information on diesel exhaust effects refutes past findings relied upon by the International Agency for Research on Cancer (IARC). Recent studies have called into question views held by IARC and others regarding the mechanisms of carcinogenesis in rats from exposure to diesel exhaust. Werner Stöber has detailed some of the relevant history. His views are supported by the available body of literature and other prominent researchers. Certain findings he discusses cast doubt on whether current views on the mechanisms of lung cancer and the current methodologies used for assessing cancer risk from diesel exhaust exposure are accurate and reliable. CARB/OEHHA should review this new literature and incorporate these findings into the TSD. (p. 6)

Response: With regard to IARC's views, the TSD merely summarizes IARC's conclusions. OEHHA staff's conclusions do not rely on IARC, and the TSD does not evaluate IARC's views. OEHHA would not ordinarily use a TSD to recommend that IARC change a finding. The revised TSD does include reviews of all relevant material that has been made available.

OEHHA staff are familiar with the history detailed by Werner Stöber. Please see our responses to his comments on the TSD. OEHHA staff considered the relevant literature referenced in the comment in revising the TSD.

10. Comment summary: CARB/OEHHA should give full consideration to the large body of German research that has been conducted on the health effects of diesel exhaust exposure, particularly the work that has been done at the Fraunhofer Institute of Toxicology and Aerosol Research in Hannover, Germany, by Dr. U. Heinrich. The German research represents some of the most recent findings with regard to the relationship between diesel exhaust exposure and health effects. The commenter attached a paper that references some recent studies by Dr. Heinrich. The commenter also attached a critical assessment of epidemiological studies on diesel exhaust exposure which provides a review of the historical development of epidemiology and unresolved issues regarding the health effects of diesel. The commenter also submitted preprints of two German chronic inhalation rat exposure studies. (pp. 6-7)

Response: The TSD now considers 13 studies and reviews by Dr. Heinrich and colleagues, including the rat studies attached to the comments and including other very recent publications. OEHHA staff respond to comments from Drs. Heinrich and Donald L. Dungworth (of Fraunhofer Institut fur Toxicologie und Aerosolforschung) elsewhere in this document.

OEHHA staff have given full consideration to all the scientific data available to us, including the German research mentioned in the comment. The critical assessment of epidemiological studies on diesel exhaust exposure referred to in the comment, is an unpublished paper -- W. Stöber, J. Misfeld, U. Abel: Lung Cancer Caused by Diesel Exhaust Gas in Inhaled Air? June 25, 1994. This paper provides some background information on epidemiological studies in general and of lung cancer in relation to air pollution. Reviews of epidemiologic studies of diesel exhaust in relation to lung cancer find shortcomings in available studies. A recent article (by Stöber and Abel) added a greatly expanded critical interpretation to a revised version of the original manuscript.

11. Comment summary: From the points outlined in the above-summarized comments, it is evident that many questions remain regarding the carcinogenicity of diesel exhaust in humans, the relevance of rat studies to human cancer risk, and the mechanisms of carcinogenesis in both rats and humans from exposure to diesel particles. The data available are insufficient to draw any conclusions regarding carcinogenicity of diesel particulates. In particular, the weak association between exposure and lung cancer risk found by Garshick, in combination with the other shortcomings of that data, make it unsuitable for quantitative risk assessment. CARB should revise its finding of carcinogenicity to acknowledge that current data are insufficient to classify diesel exhaust as a human carcinogen. On this basis, there is no justification for listing diesel exhaust as a toxic air contaminant (TAC), unless CARB believes (and can document) that health considerations other than cancer risk warrant listing diesel exhaust as a TAC. (p. 7)

Response: See responses to the specific comments above. OEHHA staff agree with the commenter that many questions remain, yet we have found the Garshick data to be suitable for use in quantitative risk assessment.

Inhalation exposure to diesel exhaust has been demonstrated to increase the incidence of lung tumors in rats. Chapter 7 of the TSD outlines uncertainties of extrapolating human cancer risk from rat lung tumor data; however, the rat lung tumor data has not been shown to be mechanistically irrelevant to human cancer risk from diesel exhaust inhalation and, with uncertainties acknowledged, provide information useful in the characterization of the potential magnitude of the human cancer risk associated with diesel exhaust exposure. Others have drawn conclusions from the available data. For example, IARC (1989) has stated that there is sufficient evidence for the carcinogenicity in experimental animals of whole diesel exhaust, and that diesel exhaust is probably carcinogenic to humans. Regarding whether diesel exhaust is a human carcinogen, the TSD thoroughly evaluates the increased relative risks of lung cancer observed in the epidemiologic studies and their association with diesel exhaust exposure. The findings and analyses presented in the TSD provide a substantial basis on which to base a decision on whether to list diesel exhaust as a TAC.

Comments of Natural Resources Defense Council (NRDC)

1. Comment summary: The commenter commends the ARB for proposing to list diesel exhaust as a probable human carcinogen. The sometimes highly technical arguments about risk assessment should not obscure the central fact that diesel exhaust is likely to be a cause of debilitating and sometimes fatal cancers, many of which occur with increasing frequency over recent decades. It would be imprudent and even callous to the people exposed to diesel exhaust to ignore the consistent evidence before us simply because risk estimates are by necessity imprecise. Diesel exhaust should be listed as a probable human carcinogen. (Testimony presented by Janet S. Hathaway, Senior Attorney, NRDC Transportation Project, before the ARB on September 14, 1994, pp. 3-4).

Response: The TSD thoroughly evaluates the increased relative risks of lung cancer observed in the epidemiologic studies and their association with diesel exhaust exposure.

The toxic air contaminant (TAC) listing process does not require labeling a substance as a "probable" or "certain" disease-causing agent. Thus, the TSD is not recommending that diesel exhaust be listed as a probable human carcinogen. All that is required for listing is a finding that a substance meets the definition of a TAC, which is "an air pollutant which may cause or contribute to an increase in mortality or in serious illness, or which may pose a present or potential hazard to human health" (or a substance listed by the U.S. EPA as a hazardous air pollutant pursuant to the federal Clean Air Act). The TSD concludes that diesel exhaust appears to meet this definition.

2. Comment summary: It is commendable that Cal/EPA is undertaking this effort to assess the risk posed by diesel exhaust. It is critical to ensure that the risk from diesel exhaust is rigorously evaluated. Because of the commonplace nature of diesel exhaust exposure, the carcinogenicity of diesel exhaust may present a serious public health problem. (p. 6)

Response: The TSD incorporates a thorough evaluation of the health effects associated with diesel exhaust. The widespread exposure to diesel exhaust justifies the effort that went into the document.

3. Comment summary: The TSD states that at least 16 possible human carcinogens are adsorbed on diesel exhaust particles, yet the risk assessment presumes that these toxic gases do not contribute to the cancer risk. The document justifies this assumption by reference to a few animal studies which appear to indicate that the cancer risk for rats from diesel exhaust is primarily from the fine particulate matter, but human beings may be, and sometimes are, more responsive to certain carcinogens than some animal species. Given the independent evidence strongly suggesting carcinogenicity of many of the organic gases in diesel exhaust, the document's failure to include the risk contributed by these gases may underestimate the risk to humans from diesel exposure. (pp. 6-7)

Response: The summary chapter of Part B does state that 16 possibly carcinogenic hydrocarbons are adsorbed on diesel exhaust particles. The risk assessment considers that these hydrocarbons

may contribute to the cancer risk posed by diesel exhaust. To clarify this, the summary chapter's statement (regarding these compounds plus three more) that a report "concluded that the total carcinogenic effect estimated for all these compounds does not account for the carcinogenic effect of the whole diesel exhaust" has been modified to say “... does not account for all of the carcinogenic effect .... “

The chapter on genotoxicity and mechanisms of action notes that components of diesel exhaust including the semivolatile phase may be mutagenic. It is a biologically plausible mechanism that mutations caused by these components may contribute to the development of cancer.

While several animal inhalation studies used filtered diesel exhaust, the risk assessment based on epidemiologic findings is for inhalation exposure to whole diesel exhaust.

4. Comment summary: It is evident that OEHHA is taking pains not to overstate the risk posed by diesel exhaust. By not estimating the additional cancer risk posed by the gaseous components of diesel fuel, the TSD's risk assessment underestimates the cancer risk to humans from diesel exposure. Benzene is a known human carcinogen, according to several sources, and formaldehyde, 1,3-butadiene and acetaldehyde are probable human carcinogens. OEHHA should, as a matter of prudent public health policy, assume that the risk from the gaseous portion is additive with the carcinogenic risk from the diesel particulates. There is precedent for such an assumption in the USEPA's assessment of gasoline. It is particularly appropriate here, since the gaseous portion includes many probably human carcinogens, and only a portion of the complex organic combustion products are known to adsorb onto the surface of the respirable exhaust particles. Assuming additivity may underestimate the total effective human risk if one or more of the components operates synergistically to magnify the cancer risk. The possibility of synergy between the constituents deserves further study in a mixture as complex and variable as diesel exhaust. (pp. 7-9)

Response: The risk assessment in the TSD is intended to address risks from diesel exhaust (engine emissions - not evaporative emissions of unused fuel). It does use particle mass as its measure of dose, yet this should not be thought to completely exclude effects caused by the gaseous components of diesel exhaust. The subjects in the human studies were exposed to whole diesel exhaust, so the gaseous components may have contributed to the disease incidence seen there, which is considered the response rate for purposes of dose-response assessment. Each of the gases mentioned in the comment is the subject of separate consideration in the Toxic Air Contaminants Program, and other gaseous components of diesel exhaust have been, are being, or may be considered separately for regulation.

OEHHA would assume additivity of risks (as suggested in the comment) while undertaking further investigation of possible synergy (as also suggested in the comment), if the risk assessment were including gaseous components of diesel exhaust in its measure of dose.

Limited research has not provided evidence for synergy with regard to carcinogenic effects of components of diesel exhaust; this is mentioned in Chapter 6 of Part B.

5. Comment summary: All of the worker studies evaluated by OEHHA were studies of men. Women also drive trucks, serve as conductors on trains, and are otherwise frequently exposed to diesel at work. The worker studies only evaluated the cancer risk to males. To extrapolate from these studies to the general population may not provide adequate protection for women, children, and infirm and elderly individuals exposed to diesel exhaust at ambient levels. Animal evidence, including some studies acknowledged in the TSD, suggests that caution in extrapolating from worker studies to the public is especially warranted in the case of diesel exhaust. Prudent public health policy should ensure that levels of diesel exhaust are protective of even the most vulnerable segments of the population, and should assume, based on the animal evidence, that women may be more susceptible to cancer from diesel exhaust than men. The TSD's risk estimate fails to consider the possibility of increased female risk from exposure, and therefore underestimates the total population risk from diesel. (pp. 9-10)

Response: Part B of the TSD now acknowledges the possibility that female humans may be more susceptible to cancer from diesel exhaust than the male workers whose experience is the main basis for the risk assessment. This is discussed in Chapter 7. Chapter 1 points out, as source of risk assessment uncertainty, the fact that the occupational studies are based on "healthy male workers." Regarding whether animal evidence suggests a need for special caution when relying on male data for diesel exhaust, Chapter 6 notes that the rat bioassay data are insufficient to determine if sex differences exist in sensitivity to the development of lung tumors in rats after exposure to diesel exhaust. Four of the seven positive diesel exhaust inhalation rat bioassays used both male and female F344 rats. Brightwell et al. (1986; 1989) reported total lung tumor incidences of 44% and 96% in males and females, respectively, in animals sacrificed after the end of the 24 month exposure period. However, mortality data were not provided, so it cannot be determined if differences in survival between the two sexes affected tumor incidence rates. Ishinishi et al. (1988) found total lung tumor incidence to be greater in males than females at the highest two exposure levels for each of the two diesel engine types tested. Mortality rates were similar for both sexes. Mauderly et al. (1986) reported similar mortality rates and total lung tumor prevalence rates for male and female rats. Nikula et al. (1995) noted that female rats were more susceptible than male rats to developing lung tumors after exposure to diesel exhaust. However, mortality rates for male rats were also greater than female rats. As described in Section 6.1.1.2 of Part B, logistic regression modeling did not show significant differences between the tumor responses to diesel exhaust or carbon black for either sex. However, slope estimate error values in the logistic regression models were large; the errors were particularly large for the males, because of their much shorter lifespan compared to the females. Lung tumor incidence in the females increased rapidly towards the end of their lifespan, when most of the males had died of other causes. Also, the lack of lung tumors in the control females may have increased the estimated slopes for the treatment group females. Nikula et al. stated that these factors make it difficult to determine if there were true sex differences in neoplastic incidence or differences in the responses.

In health risk assessment, we do not ordinarily incorporate a quantitative uncertainty factor specifically to account for potential differences between the sexes in susceptibility to carcinogenic effects (or to-account for differences in such susceptibility in children, the elderly or infirm). To some extent, the possibility of such differences is offset by the health-protective

assumptions and procedures that are used in cancer risk assessments (e.g., the assumption that humans are at least as sensitive as the most sensitive tested animal species, strain and sex, or the use of linearized models and 95% upper confidence limits). In a 1990 TSD regarding vinyl chloride, DHS recommended use of a potency factor based on female mouse data that was substantially (more than four times) greater than the highest potency factor estimated from human data and the human data were from a male occupational group. (A sex difference was noted in rats, which were also, like the mice, more susceptible than human workers: female Sprague-Dawley rats were approximately 3-fold more susceptible to liver angiosarcoma from vinyl chloride than were males.) With diesel exhaust, however, the human data (although from males) suggest a potency factor that is greater than any of the potency values derived from female or male rodent studies. Thus it would not be prudent to rely solely on rodent data to protect human health from diesel exhaust.

6. Comment summary: The human exposure studies relied on in the TSD only included workers with at least 10 years of experience in the railroad industry, thereby excluding people whose age or health conditions prevent them from continuously working in the industry. The two main studies by Garshick et al. cannot be assumed to directly reflect the cancer risk for the population at large. The general public may well have a greater cancer risk than the workers in these studies. The studies were limited to workers with 10 or more years in the railroad industry who qualified for retirement benefits. The "healthy worker effect," or better health among workers than the general public, is particularly probable for workers in an industry with a relatively successful history of collective bargaining for benefits') such as the railroad industry. (pp. 10-11)

Response: The risk assessment chapter has been modified to include a discussion of "the healthy worker effect" and its relevance to the Garshick et al. data. The factors cited in the comment (employment-length minimum, good health benefits) can indeed contribute to a healthy worker effect.

7. Comment summary: The worker studies relied on in the TSD are inherently limited in providing little information about possible effects for children, for the elderly, and for people with chronic illnesses (such as emphysema, asthma and bronchitis) or depressed immune systems. To the extent that these groups are slower to remove particles from deep lung tissues, they are likely to have greater risk from diesel exhaust exposure than long-term workers, because the time needed to clear small particles from the lungs appears to be a factor increasing the risk of tumor development. (pp. 11-12)

Response: Part B of the TSD (Chapter 4 and Appendix A) addresses the possibility that human subpopulations may be more susceptible to the adverse health effects of diesel exhaust due to factors such as those mentioned in the comment (chronic illnesses, depressed immune systems and slow clearance of particles from the lungs). Recent research has shown the existence of subpopulations sensitive to allergic and asthmatic reactions from diesel exhaust. These studies (Diaz-Sanchez et al., 1994; Takenaka et al., 1995; Wade and Newman, 1993) are now cited in Chapter 4. Insufficient data were available to directly account for these factors in the TSD's risk assessment for diesel exhaust. However, the likely existence of sensitive subpopulations, is one reason for taking a health-protective approach to assumptions and procedures for use in risk

assessment. The data available for diesel exhaust indicate that humans are more sensitive than animals to lung cancer associated with exposure. The lack of data on sensitive populations limits our ability to answer some questions.

8. Comment summary: The TSD notes that cancers involve a latency period of a number of years between damaging exposure and development of cancer. Yet because exposure in the general population to diesel exhaust begins at a very early age, direct extrapolation from traditional animal exposure studies and .worker studies may underestimate the risk to the public. Most of the animal studies involving diesel exhaust involve animals which are already "teenagers." (p. 12)

Response: Two sections of Part B's risk assessment chapter now acknowledge this potential source of bias. The section that provides animal bioassay-based risk estimates (Section 7.2) now mentions the extrapolation issue raised by studies that wait until animals are 15 weeks of age ("teenagers" per the comment) to begin exposure. The human data-based risk assessment (Section 7.3) now includes an expanded discussion of the representativeness of worker cohorts.

With regard to extrapolation from the rat data, the fact that exposure began at 17 weeks of age for Mauderly et al. (1987)'s rats was entered into the model for determination of q_1^*. If one applies strict proportionality, and considers 2 years (104 weeks) to be a standard rat lifespan and 70 years to be a standard human lifespan, a 17 week-old rat is equivalent to a 11-1/2 year-old human, not quite a teenager. Nevertheless, the comment's point is still valid.

9. Comment summary: The general population is exposed to diesel exhaust and a variety of carcinogens simultaneously. Animal studies in which diesel exhaust was the only known carcinogenic exposure may not be properly representative of the complex exposures to which most people are subject. Worker studies are far more likely to reflect the multiplicity of exposures to carcinogens which real people routinely receive. Because the diesel exhaust risk assessments derived from the best occupational studies reveal a higher risk than those based on animal data, it is paramount that Cal/EPA continue to use worker studies as the basis of human risk assessment. However, there should be a safety factor introduced to account for the many chronic carcinogenic exposures which occur simultaneously throughout a lifetime. A protective policy for diesel exhaust exposure cannot be based on the obviously fanciful assumption that humans live in a pristine world where diesel exhaust is our only cancer danger. (p. 15)

Response: The TSD does continue to use worker studies as the primary basis of human risk assessment.

Cancer risk assessments do not ordinarily include a safety factor to account for the many carcinogenic exposures which occur simultaneously throughout a lifetime. Additivity of risks, rather than synergy, is usually assumed. Available data are too limited to support a variance from this assumption. A less-than-additive outcome of multiple exposures (negative synergy) is also a possibility that cannot be ruled out.

10. Comment summary: Atmospheric transformation may increase the mutagenicity and carcinogenicity of diesel exhaust. Smog chamber studies suggest that the gas phase is activated into a more potent mutagen by atmospheric processes, including irradiation. Unless the effects of atmospheric transformation are considered, OEHHA's analysis may underestimate the true cancer rate from diesel. (pp. 15-16)

Response: The TSD's risk assessment uses particle mass as its measure of dose. As discussed in the Part B, Section 7.1, this measure is what was used in the studies used to estimate carcinogenic risk. Thus, particle mass is a surrogate measure of exposure for all carcinogenic risks of direct exposure to diesel exhaust. Because of lack of data on diesel exhaust, the risk assessment is not specifically intended to address risks posed by atmospheric transformation of gaseous components of diesel exhaust. In this regard, the analysis may indeed represent something of an underestimation of the true cancer rate from diesel. This could be a useful area of future research. This source of uncertainty is now mentioned in Chapter 7. See also the ARB Responses to Part A Comments, where atmospheric transformation is discussed.

11. Comment summary: Cal/EPA should reevaluate the cancer risk from diesel exhaust by considering the entire range of exposures, not just a "statewide average." A risk estimate must be done for those Californians who live and work in or near places with the highest diesel concentrations. (pp. 16-19)

Response: The summary chapter of Part B now includes a range of risk estimates based on exposure estimates provided by the Air Resources Board. This includes risk estimates for areas of intense exposure. OEHHA staff agree that, in addition to the statewide average, it is important to provide information that is relevant to the Californians who live or work in or near places with the highest concentrations of diesel exhaust.

12. Comment summary: Further investigation of the non-cancer health effects of diesel exhaust is clearly warranted because many of the constituents of diesel exhaust are known to harm exposed animals even aside from cancer effects. These constituents include benzene, formaldehyde, acetaldehyde, 1,3-butadiene, and diesel particulate matter, which cause serious and damaging non-cancer effects ranging from respiratory irritation to reproductive disorders and immune suppression. (pp. 20-21)

Response: Constituents of diesel exhaust do include many chemicals, including those mentioned, that cause a variety of non-cancer health effects when present in sufficient concentrations. Many of these effects do not stem from particle-overload phenomena. OEHHA staff have expanded discussion in the TSD of non-cancer health effects associated with diesel exhaust to include recent studies showing immunologic, allergic, and pulmonary effects. As mentioned above (see response to comment 4), separate regulatory processes are also addressing the non-particulate constituents mentioned in the comment.

13. Comment summary: Despite the many ways in which the TSD's risk assessment is likely to underestimate the true risk for at least some important segments of our population, the cancer risk described in the assessment even for the average person should cause serious concern. The

public deserves prompt action to reduce diesel exhaust in order to prevent needless suffering from cancers and other diseases. (pp. 21-22)

Response: We have sought to provide a characterization of the potential health effects of diesel exhaust that will prove useful for the Air Resources Board during the identification and control phases of the Toxic Air Contaminant Program. ARB has been very successful in identifying appropriate measures to protect public health.

Comments of Gregory P. Nowell, SUNY Albany

1. Comment summary: The TSD is "carcinocentric." That is, it gives appropriate attention to the carcinogenic properties of diesel exhaust, but inadequate attention to the probably noncarcinogenic effects documented by Schwartz and others, which are discussed in a special Appendix B of Part B. The research by Schwartz et al. finds correlation between particulate matter (PM) episodes and (non-cancer related, it is reasonable to suppose) mortality in numbers far in excess of cancer-related mortality. The physiological mechanism behind the mortality spikes is not known. It may be that that some one of the gaseous or particle-adsorbed constituents of diesel exhaust is a factor; we would expect it to be a factor at least in proportion to the diesel fraction's contribution to the total particulate inventory, but it may be that there is a heightened deleterious health effect due to the specifics of diesel exhaust's composition. Street canyon effects and other factors which increase individual exposure (such as being stuck in traffic in back of a diesel engine) may be disproportionately worse during PM episodes when overall levels are high. The scale of the effects found by Schwartz et al. suggests that the quantity of PM (in the short term) may be as important as the quality of the PM. The "bulk sources" of PM are probably important. Secondary particulate formation resulting from diesel exhaust is one such bulk source. It could be medically more important than other non-exhaust PM sources such as road dust because of the chemical reactivity of PAN. NOx emissions are of great consequence from the PM point of view, exclusive of their additional role in ozone formation. Since both primary particulate and secondary particulate are chemically more reactive (in the air and in the body) than a number of other common particulates, the risk-weighted importance of primary and secondary particulate in the inventory could be quite large. (Letter, dated July 6, 1994, pp. 1-3)

Response: We have expanded the TSD's discussion of non-cancer effects in general in Chapter 4 and, with respect to particulate matter in general, in Appendix B. We agree with the comment that there may be important non-cancer effects of diesel particles, as a constituent of both PM10 and PM2.5 (or fine particles), and that the effects per unit may be greater than those per unit of other PM10 because of factors relating to composition of the particles. We also concur with the statement that the biologic mechanism for these effects are not well characterized at this time. People living or working on major streets may experience higher exposure due to "canyon effects." Any epidemiologic study of mortality or morbidity with a sufficiently wide cachement area would include these people. There is evidence from the EPA Staff Paper on PM10 (Review of the National Ambient Air Quality Standards for Particulate Matter, Policy Assessment of Scientific and Technical Information. OAQPS Staff Paper, EPA 452\-96-013, July 1996) that, quantitatively, there may be significant mortality and morbidity effects associated with current exposure to PM10 or PM2.5. The risk analyses presented in the paper are based on estimates of

change in PM10 exposure from "current" levels to some standard, and on dose-response functions from the epidemiologic literature (relating exposure to particulate matter to various health outcomes). For L.A. County, the paper reports that current PM10 exposures (both acute and chronic) in L.A. County are associated with 2800 deaths per year, 1200 hospital admissions, and over 40,000 incidences of lower respiratory symptoms in children age 8 to 12. Estimates apparently were not provided for other known non-cancer health effects such as asthma attacks, acute and chronic bronchitis, and restrictions in activity.

The TSD mentions general particle effects so that they can be considered along with specific diesel exhaust effects by risk managers seeking to understand the complete picture. The report does not discuss those effects in any detail or include a risk assessment of them because this is a report to support toxic air contaminant (TAC) identification of diesel exhaust per se, and the general particle effects are being treated in connection with ambient air quality standards for particulate matter and related regulations. The TSD now cites the U.S. EPA Staff Paper in Section 1.1 and in Appendix B of Part B. The same reasoning applies for nitrogen dioxide, for which there are also ambient air quality standards. The situation is more complicated with regard to PAN and other substances that derive from numerous types of sources and are suspected of having some harmful effects on health when their concentration is at high enough levels, but do not have ambient air quality standards or other action levels. If such substances are present in air at levels thought to cause adverse effects, those substances should be addressed individually, perhaps as subjects of separate TAC identification proceedings.

The TSD uses particle mass as a surrogate measure of exposure for all risks of direct exposure to diesel exhaust. Because of lack of adequate data on diesel exhaust, the TSD does not specifically address risks posed by atmospheric transformation of diesel exhaust or secondary particulate and secondary particulate matter precursors such as NOx and hydrocarbons. In this regard, the TSD may indeed not describe completely the cancer and non-cancer health risks posed by diesel. This could be a useful area of future research. This source of uncertainty is now mentioned in the TSD. See also the ARB staff responses to comments, where atmospheric transformation and secondary particulates are discussed.

2. Comment summary: Part B should include quantitative estimates of the probable mortality rates due to PM episodes in California. (p. 2)

Response: Ambient PM, to which diesel exhaust is a major contributor, has been consistently associated with increases in both morbidity and mortality. The findings indicate a serious public health problem. We understand that PM is to be addressed by ambient air quality standards and related (non-TAC program) regulations. Thus, the TSD for diesel exhaust does not include estimates for the increased mortality attributable to the non-carcinogenic effect of PM (or PM2.5) or diesel exhaust as a component of PM (or PM2.5).

3. Comment summary: Part B should also contain information on PAN and more explicitly discuss the disturbing questions raised by the Schwartz et al. data and make some serious recommendations about what can be done in the next five years to clarify them. In particular, the linkages need to be made between the elevated mortality rates and their medically determined

causes. The revised TSD should not say anything like "no regulations should be undertaken until more studies have been made," however, because the Schwartz et al. studies point to a "clear and present danger" which the current draft TSD does not adequately address. (p. 2)

Response: As suggested in response to Comment 1, if PAN or other substances that derive from numerous types of sources are present in air at levels thought to cause adverse effects, those substances should be addressed individually, perhaps as subjects of separate TAC identification proceedings.

We have updated Appendix B of Part B to include discussion of recent studies by Schwartz and others linking exposure to particulate matter to both mortality and morbidity. Studies have been conducted to include estimates of the linkage between cause-specific mortality and particulate matter. Two major uncertainties about these effects continue to exist. First, what is the amount of life-shortening involved in these effects? Second, what are the implications for longer term exposure to particulate matter? These questions can only be resolved through additional research. We agree that risk management decisions are typically made in the presence of some uncertainty, and that available studies do indeed point to a high likelihood of some risk from particulate matter. Part B of the TSD therefore does not make statements like "no regulations should be undertaken until more studies have been made." The TSD focuses on the health effects of diesel exhaust. This limited scope should not be interpreted as a caution against separately regulating particulate matter in the absence of further studies.

4. Comment summary: The TSD should admit that it is plausible that other PM sources, such as agricultural dust laced with insecticides, or charbroiled steak fumes laced with combusted beef growth hormones, are also harmful. In the long run, the control strategies and research agendas needed to develop them will be better if we address all the dimensions of the problems. (p. 3)

Response: Part B of the TSD (Appendix B) now contains a statement which points out that emissions from other PM sources may pose health risks similar to those posed by diesel. Comparative risk analysis of various PM sources is not within the scope of the TSD. Nevertheless, OEHHA staff agree that a separate risk assessment and comprehensive research programs on PM would be useful.

Comments of Gunter Oberdörster, University of Rochester

1. Comment summary : The section in the health risk assessment document on non-carcinogenic effects and endpoints should include and also emphasize more endpoints, in particular when considering endpoints for risk estimation and deriving an RfC. In the document, the rat study by Ishinishi et al. (1988) was used to derive an RfC of 5 $\mu g/m^3$ based on observed hyperplastic lung lesions. However, it appears that both impairment of lung clearance and chronic alveolar inflammation are more sensitive non-cancer endpoints. A recent two-year diesel inhalation study in rats performed at the Fraunhofer Institute in Germany included measurements on lung clearance function as well as relevant lung lavage parameters. A W.H.O. Review Group meeting, chaired by the commenter, in June 1994 discussed these data. The commenter, working with Dr. Chao Chen of USEPA, has used the Fraunhofer and Ishinishi et al. data to derive guidance values

for non-cancer endpoints. In addition to the NOAEL approach, in analogy to the benchmark dose approach, these workers arrived at a benchmark concentration for three different non-cancer endpoints which gave guidance values ranging from 2 to 14 Ug/M3. The TSD should include and discuss these additional non-cancer endpoints in more detail, in consideration of a draft from W.H.O. Including the non-cancer endpoints in the TSD would strengthen the evidence for diesel exhaust being a toxic air contaminant (TAC). (Letter dated August 9, 1994, pp. 1-2)

Response: Chapter 4 of the TSD has been updated and revised to include many of the endpoints mentioned by the commenter. The benchmark analyses conducted by WHO in 1994 have been included, along with similar calculations performed by OEHHA staff. The resulting range of chronic, non-cancer health values is consistent with the range of values presented by the commenter, W.H.O., and USEPA. In addition to these analyses, Chapter 4 now includes discussion of recent human and animal studies on the influence of diesel exhaust on immunologic parameters in the lung and upper airways.

2. Comment summary: The TSD should give more emphasis to the particle effect with respect to tumor induction in rats. Studies now show that inhalation of a number of supposedly inert particles, such as TiO_2, carbon black, talc, do induce lung tumors in rats during chronic exposures at relatively high concentrations. These lung tumors have been generally associated with a state of "lung particle overload". This is important since the particle effect alone can fully explain the lung tumor incidences seen in diesel-exposed rats. Additionally, this concept of lung particle overload implies that a threshold in terms of lung burden or chronic exposure concentration exists below which no overload-associated effects, the hallmark of which is impaired lung clearance, occur, and this issue of a threshold should be discussed more in the health risk assessment document. The evidence of genotoxicity of the diesel exhaust found in certain in vitro studies is not a strong argument against a threshold since particles devoid of genotoxic organic materials also induce tumors in the rats. Furthermore, inhalation of PAH-rich emissions alone induces lung tumors in rats only at concentrations which are several orders of magnitude higher than the PAH levels associated with diesel exhaust particles in the chronic diesel studies. In addition, studies showing that DNA adducts were also induced after carbon black exposure point to non-specificity of the adduct formation.

With respect to humans exposed to diesel exhaust it appears that for the development of lung cancer a particle overload-associated effect could not be the cause. It is entirely possible that at the lower exposure concentrations experienced by human workers a PAH effect may be present and that only at very high concentrations as used in the rat inhalation studies the particle effect becomes operative when most of the PAHs do not interact with target cells but are rapidly eliminated. (p. 2)

Response: The current (new) draft TSD describes studies by Heinrich et al. (1995) and Nikula et al. (1995) which compared rat lung tumor incidence rates after inhalation exposure to diesel exhaust, carbon black or TiO_2. The TSD also discusses the hypothesis developed from these studies that chronic inflammation resulting in macrophage and/or neutrophil-induced oxidative DNA damage resulting in mutations may be mechanistically important in the induction of lung

tumors, and that cell proliferation may be mechanistically important to the promotion of lung tumors, in rats exposed to high levels of diesel exhaust by inhalation.

Although no mechanism has been established to account for the increased rates of lung tumors in diesel exhaust-exposed workers, it has been proposed that any modeling of human cancer risk from rat lung tumor data should include an exposure threshold below which tumor induction would not occur. The lower levels of exposure to diesel exhaust associated with lung cancers in the epidemiological studies do not appear to involve particle overload of the human lung. Therefore, it does not appear reasonable to predict the human lung response using the particle overload assumptions. Therefore, if the rat lung overload/threshold assumption held, the rat lung tumor data may not be a reliable predictor of any potential human cancer risk due to diesel exhaust inhalation.

The ability of particulates such as carbon black which lack direct genotoxic potential to cause lung cancer in the rat model does suggest that genotoxicity may not be required for the observed rat lung response to diesel exhaust. However, there may still be no dose response threshold. The proposed overload mechanism includes chronic inflammation and associated production of inflammatory cytokines and increased cell proliferation. As noted in a recent paper by Gaylor and Zheng (1996), (1) a threshold dose is questionable if a carcinogen acts via a cell receptor, (2) even a nongenotoxic carcinogen that increases the cell proliferation rate by augmenting an endogenous mechanism is not likely to have a threshold dose, and (3) dose response curves for cell proliferation and tumor incidence do not necessarily mimic each other. Thus, elements of the particle "overload" mechanism may operate at low levels of exposure in humans. It is also possible that other particle effects, such as solid-state catalysis, operate with no threshold in humans.

The possibility cannot be excluded that genotoxicity, perhaps due to the PAH and nitroPAH content of diesel exhaust, also plays a role in the induction of lung tumors in rats at lower levels of diesel exhaust. This mechanism would probably be relevant to the observed human cancer risk, and would not be expected to have a threshold of action. With regard to PAHs, note that although tumors from PAH-rich emissions may have been observed only at high levels in certain animal experiments, tumor induction by genotoxic material such as PAHs is not expected to have a threshold whether or not some (but not all) of the material is removed from lungs by particle clearance mechanisms. Chapter 5 of Part B describes extraction under physiological conditions of mutagens from diesel exhaust.

With regard to DNA adducts, Chapter 5 describes the occurrence of a specific DNA adduct in rats exposed to diesel exhaust which was not observed in rats exposed to carbon black. The chapter also describes increased lymphocyte DNA adducts in humans occupationally exposed to diesel exhaust.

The rat lung tumor data have not been definitely shown to be mechanistically irrelevant to human cancer risk from diesel exhaust inhalation and, with uncertainties acknowledged, can contribute information useful in the characterization of the potential magnitude of the human cancer risk associated with diesel exhaust exposure.

3. Comment summary: The conclusion of the health risk assessment document that diesel exhaust is a human carcinogen will certainly lead to some objections. Since the 1989 IARC evaluation, the evidence has been strengthened somewhat from epidemiological studies. However, the commenter's W.H.O. Review Group still concurred with the overall IARC evaluation that diesel exhaust is probably carcinogenic to humans. The commenter agrees that diesel exhaust appears to meet the definition of a TAC, but the commenter is a bit more cautious than the draft TSD with respect to the characterization of diesel exhaust as a confirmed human carcinogen. (pp. 2, 3)

Response: Regarding whether diesel exhaust is a human carcinogen, the TSD thoroughly evaluates the increased relative risks of lung cancer observed in the epidemiologic studies and their association with diesel exhaust exposure. The TSD no longer suggests a category determination.

4. Comment summary: The commenter's W.H.O. Review Group concluded that there are no quantitative data from the epidemiological studies suitable for estimation of human risk. The commenter mentions this because Dr. Garshick was one of the members of the group and he specifically agreed with this assessment and did not think that his data set was suitable for performing a quantitative risk assessment. The relative risk of lung cancer in all of the epidemiological studies was generally low, and Dr. Garshick as well as the other members concluded that such relative risks are more susceptible to chance, to the effects of unmeasured confounding factor's and to the difficulty in accurately adjusting for known confounding factors. The evidence from epidemiology for diesel exhaust being a human carcinogen is still 1-iimited; however, if the classification of a human carcinogen is made for other reasons it becomes a different matter. (pp. 2-3)

Response: Since the 1994 publication of the draft TSD, Dr. Garshick has given OEHHA staff helpful suggestions regarding our use of his cohort study (1988) data in quantitative risk assessment. OEHHA staff recently asked Dr. Garshick for assistance in responding to comments such as this one. We asked for his view of the uses to which we have put his data, and we specifically gave him an opportunity to express the opinion, if he held it, that we had misused his data. In response, he reaffirmed his position in a 1994 review letter to OEHHA staff. In that letter, he concluded that "the strength of an assessment of risk depends on the assumptions that go into it. You have made a number of assumptions that yield values of unit risk somewhat greater than animal studies, but lower than others using human epidemiologic data. In the end you have to be satisfied with these assumptions. Perhaps it would be better to use a range of potencies as the background for regulating diesel exhaust since considerable assumptions need to be made to use the current human-based data." The TSD now emphasizes a range of risk estimates, as advocated by Dr. Garshick.

In regard to the low values of relative risk in the Garshick et al. (1988) cohort study: Low values of relative risk are susceptible to both chance and confounding. Chance would tend to bias the result toward the null, tending to diminish statistical significance. Because Garshick et al. (1988) found statistical significance, that should not be a problem, except possibly diminishing the actual effect.- Confounders, whether measured or unmeasured, could be a problem and require

vigilance to avoid. Age and calendar year were controlled, though smoking was not directly controlled. The argument on smoking, undoubtedly the most potent source of possible confounding, is that the study relied on auxiliary information about railroad workers at that time from the Garshick et al. (1987a) case-control study. The case-control study found that smoking adjustment had a negligible effect on risks attributed to diesel exhaust. So the same should hold for the cohort study, the design of which should minimize any smoking effect but cannot preclude an effect. The meta-analysis included in the current draft Part B of the TSD provides a strong indication that the statistically significantly elevated rates of lung cancer observed in the diesel exhaust epidemiology, although small when expressed as relative risks, are elevated due to an effect of diesel exhaust and cannot be explained solely by chance or confounding.

5. Comment summary: Based on evidence from rats, a W.H.O. document arrives at a range of unit risk estimates with a geometric mean that is lower than that derived in the draft TSD. Interspecies extrapolation should be viewed very cautiously. The validation of a specific extrapolation model is very difficult and large uncertainties usually have to be considered. These uncertainties should be more clearly stated in the TSD. The W.H.O.-derived risk estimates should make the TSD's authors aware of the differences in results using certain different models (a specific lung extrapolation model, as in the W.H.O. document, or an unspecific model, as in the TSD). (p. 3)

Response: For both cancer and non-cancer endpoints, the TSD now includes analyses of multiple animal studies and reports a range of values for unit risk and reference concentrations. OEHHA staff have considered the W.H.O. document (see Chapter 4 of Part B) and are aware that different models can give different results. Chapter 7 now includes discussion regarding considerations for interspecies uncertainty in estimating human cancer risks from rat lung tumor data.

Comments of the Sierra Club

1. Comment summary: Further investigation would find even greater risks from diesel exhaust to public health and the environment than found by the TSD. The assessment of the public health dangers of diesel exhaust should be broadened to more carefully consider evidence of health and environmental impacts linked to certain studies (e.g., a study by Physicians for Social Responsibility) and exposure factors. (Letter from Bonnie R. Holmes, Air Quality Consultant, Sierra Club California, dated September 30, 1994, pp. 1-2)

Response: As suggested in the comment, the non-cancer effects of respirable particles may contribute to risks that are greater than the risk estimates for diesel exhaust that are detailed in the TSD. The TSD mentions general particle effects to place in perspective the effects of diesel exhaust with those of its components. The updated TSD Part B has a summary of the general particle effects (Appendix B). The TSD does not discuss those effects in any detail or include a risk assessment of them because the TSD focuses on the identification of diesel exhaust per se as a toxic air contaminant (TAC). In comparison, the report by the Physicians for Social Responsibility addresses particulates more broadly as issues of air quality standards. The general particle effects are being treated separately in connection with ambient air quality standards for

particulate matter and related regulations by Cal/EPA and the US EPA. The TSD now cites the U.S. EPA Staff Paper on PM10 in Section 1.1 and in Appendix B of Part B.

2. Comment summary: The TSD should factor health impacts from secondary particulates into quantitative risk estimates. (p. 2)

Response: The TSD's risk assessment uses particle mass as its measure of dose. As discussed in the TSD, Section 7.1, this measure is what was used in the studies used to estimate carcinogenic risk. Thus, particle mass is a surrogate measure of exposure for all carcinogenic risks of direct exposure to diesel exhaust. Because of lack of data on diesel exhaust, the risk assessment is not specifically intended to address risks posed by atmospheric transformation of gaseous components of diesel exhaust. In this regard, if diesel exhaust is transformed to more strongly carcinogenic substances, the analysis could represent something of an underestimation of the true cancer rate from diesel. This could be a useful area of future research. This source of uncertainty is now mentioned in the TSD. See also the ARB staff responses to comments, where atmospheric transformation and secondary particulates are discussed.

3. Comment summary: The TSD should include additional investigation and consideration of non-cancer impacts from diesel exhaust. (p. 2)

Response: The revised and updated TSD discusses additional human and animal studies and contains expanded discussion of analyses based on the Ishinishi (1988) rat study, including discussion of the non-cancer risk calculations by USEPA and W.H.O. OEHHA's in-house calculations from the Ishinishi study are provided for comparison with those conducted by USEPA and W.H.O. Summaries of recent case reports of asthmatic reactions and experimental studies of allergic responses in humans have also been added. .

4. Comment summary: The TSD should include more extensive investigation into recent scientific evidence showing disturbing linkages between episodes of high particulate pollution and mortality, and quantitative estimates of the probable PM10 mortality rate in California. (p. 2)

Response: A more extensive investigation of PM10 mortality rates in California is beyond the scope and purpose of this document.

5. Comment summary: The TSD should investigate the cumulative and synergistic impacts of exposure to diesel exhaust in combination with other cancer-causing substances, ambient air toxics, criteria air pollutants, and airborne particulates. (p. 2)

Response: Such an investigation would be beyond the ordinary scope of a Toxic Air Contaminant Program TSD. The diesel exhaust TSD focuses on the impact of diesel exhaust. Although an investigation of cumulative and synergistic impacts of air pollutants would be of interest to the commenter and other parties, we cannot provide a comprehensive treatment of these matters in the diesel exhaust TSD. OEHHA staff are not aware of research findings that might sufficiently resolve the issue of synergistic impacts, and a compilation of information with

regard to other air pollutants would be resource-intensive and detract from the focus of the diesel exhaust TSD.

6. Comment summary: Further investigation should be conducted to assess the impacts of diesel exhaust on sensitive populations, including the elderly, children, persons with pre-existing heart and lung conditions, and athletes. (p. 2)

Response: Part B of the TSD (Chapter 1) now acknowledges as a limitation of the epidemiological information that it is based upon occupational studies whose cohorts (i.e., healthy white males) do not fully represent the human population. The document does address the possibility that human subpopulations may be more susceptible to the adverse non-cancer health effects of diesel exhaust. The likely existence of sensitive subpopulations is one reason for taking a health-protective approach to assumptions and procedures for use in risk assessment. With respect to non-cancer health effects an additional safety factor is used to account for differences in intraspecies sensitivity. The data available for diesel exhaust indicate that humans are more sensitive than animals to lung cancer associated with exposure. Although the lack of data on sensitive populations limits our ability to answer some questions, it is fortunate that developing children and the elderly have not had the same history of exposure to diesel exhaust as the occupational groups studied.

Comments of Werner Stöber
(Visiting Scientist, Chemical Industry Institute of Toxicology)

1. Comment summary: The draft TSD Part B is, by spirit and diction, a remarkable example of where something next to nothing is made into something very serious. It is one of the most biased, distorted and outdated documents the commenter has seen in a long time. It ignores important information that, by now, is two to three years old and has significant impact on its line of reasoning. Every conscientious scientist familiar with the issues will agree that we are by no means ready for final conclusions based, as are those of the document, on scientific data of the late 1980s. We now can ask more sophisticated questions than we asked in the late 1970s. (Comments dated August 22, 1994, pp. 1-2)

Response: OEHHA staff do not agree that the TSD overstates the dimensions of the problem. The potential for bias and distortion in the TSD is limited because, first, we have analyzed the available scientific data according to standard risk assessment methodologies, second, we have sought extensive peer review, and third, we received a wide range of input from the public, academia, and industry and other groups. The current draft TSD represents an improvement over the 1994 draft in large part due to the thorough public comments sought and received.

With regard to final conclusions, regarding whether diesel exhaust is a human carcinogen, the document no longer suggests a category determination. The TSD thoroughly evaluates the increased relative risks of lung cancer observed in the epidemiologic studies and their association with diesel exhaust exposure.

2. Comment summary: In Chapter 7 of Part B, much ado is made as to whether the atmospheric exposure concentrations or the actual lung burdens are the right surrogate for dose, and both definitions are used in the calculations. However, these definitions are, at best, applicable in case of conventional chemical carcinogenesis. The first definition crudely ignores alveolar clearance, and both do not address heterogeneous solid state catalysis, although this is the only way of chemical interaction between an insoluble particle and its host. The mathematical models employ deposited particle mass per body surface area as a surrogate for relative dose with no regard to the target tissue. However, this may only be valid if the particles carry a certain amount of quickly bioavailable soluble substances for chemical carcinogenesis into the lung. This would not apply to solid state catalysis, which would relate to the specific surface area of the practically insoluble particles, to the accumulated retention in the vicinity of the target tissues and to the residence time in that location. the result would be a time integral over the time-dependent accumulation of particle surface in a specific pulmonary location. This is very similar to irradiation doses from deposited radioactive particles. (pp. 3-4)

Response: There are potentially several mechanisms simultaneously contributing to the overall observed carcinogenicity associated with diesel exhaust. The genotoxicity of diesel exhaust particles and the organics adsorbed on them is well documented. It is not at all clear that solid state catalysis is required for the genotoxic effects to occur. Nevertheless, numerous animal studies indicate that particulate mass, either atmospheric concentration or lung burden, is an acceptable surrogate for the effective dose of the exhaust particle. Furthermore, it has not been possible to measure total particulate surface area, and there is no conventionally accepted model for estimating this parameter.

Several mechanisms other than solid state catalysis have been proposed to explain diesel exhaust-induced lung tumors (see Part B, Chapter 5). Oxidative DNA damage studies (Chapter 5) and rat carcinogenicity bioassay data with diesel exhaust, carbon black and TiO_2 (Chapter 6) suggest something other than a solid state catalysis model (although they do not rule out a role for solid state catalysis). It is possible that genotoxicity due to the PAH and nitroPAH content of diesel exhaust plays a role in the induction of lung tumors in rats at lower levels of diesel exhaust. This mechanism would probably be relevant to human cancer risk, and would not be expected to have a threshold of action. (Chapter 5 describes extraction under physiological conditions of mutagens from diesel exhaust, as well as increased lymphocyte DNA adducts in humans occupationally exposed to diesel exhaust.) Although the model suggested in the comment would have a result similar to models for irradiation doses from deposited radioactive particles, it is not clear that the action of diesel exhaust should be modeled like the action of radioactive particles.

3. Comment summary: The first tumors observed in rat studies of airborne diesel soot were mostly of a benign rat-specific type which some pathologists would prefer to call cysts. The tumors observed in rats might be a rat-specific phenomenon. For quantitative human risk assessment, regardless of any California Guidelines, if there is nothing else but several studies with values of relative tumor incidence depending on several exposure concentrations during lifetime inhalation studies with rats, the commenter refuses to take the TSD's extrapolation to man to be good science. (pp. 2-4)

Response: Some of the tumors observed in rats might be rat-specific, as the commenter points out. The TSD has been revised to include an expanded discussion of the uncertainties involved in the extrapolation of human cancer risk from rat lung tumor data. Squamous cysts have been removed from the TSD's final quantitative extrapolations from animal data.

4. Comment summary: The draft document makes reference to Mauderly et al. studies as furnishing excellent data for use in the multistage models. However, it does not mention the huge differences in tumor data between Fischer 344 rats in Albuquerque, NM, and those in Geneva, Switzerland. With these variations in data, the commenter would feel very uncomfortable as a risk assessor. (p. 4)

Response: The analyses of the Geneva (Brightwell et al. 1986, 1989) data have been included in Section 7.2 of the TSD. The q_l^* values differ by less than 3-fold between the Geneva and Albuquerque (Mauderly et al. 1987) studies; a magnitude of difference not uncommon between such studies, and not a difference OEHHA staff would describe as huge. Furthermore, an illustration of the consistency of the results of various rat bioassays is given in Stöber and Mauderly (1994), in their Figure 18, which shows five studies that are reasonably consistent in the lifetime tumor incidence rates. The variability of these results is also now the subject of a comparative quantitative analysis in the TSD.

5. Comment summary: The advantage of available experimental lung burden data for the Mauderly studies does not provide a significant edge over the other studies, because the logistic regression did not permit a distinction of the two tested dose surrogates. Maybe this is the result of their inadequacy for solid state catalysis. The application of the Mauderly data to the Weibull and the Moolgavkar models shows that this inadequacy persists. The calculations do not permit a discrimination between the two trial dose surrogates. In addition, the model calculations determine in all four cases the no-effect level to be zero, which may go well with the risk assessors. However, the calculations also imply in all four cases that the latency period is zero, which is clearly inconsistent with the experimental data of very late occurring carcinogenic effects in the rats. (p. 4)

Response: There are potentially several mechanisms simultaneously contributing to the overall observed carcinogenicity associated with diesel exhaust. The genotoxicity of diesel exhaust particles and the organics adsorbed on them is well documented. Nevertheless, numerous animal studies indicate that particulate mass either atmospheric concentration or lung burden is an acceptable surrogate for the effective dose of the exhaust. particle.

As stated in Part B's Chapter 7, the Mauderly et al. (1987) study was chosen largely because it was the only study that contained complete time-to-tumor data for individual animals throughout their lifetime. The fact that both lung burden and air concentration measures of dose allow similar estimates of risk does not invalidate either of the two surrogates for dose, since there is no a priori reason that risk estimates based on lung burden should be statistically different from those based on air concentration.

With regard to latency, the four different analyses of the Mauderly et al. (1987) data did give the results of zero latent period between carcinogenesis and detection, within the precision of bioassay data. The definition of latency in these models is the time between carcinogenesis and detection of the tumor. It is true that the observed tumors mainly appeared long after the start of exposure.

6. Comment summary: The summary of the draft document erroneously allocates to Brightwell et al. (1989) the finding of a higher incidence of malignant tumors in mice for filtered diesel exhaust than for unfiltered exhaust. It should be ascribed to Heinrich et al. (1986). (p. 4)

Response: The erroneous attribution has been corrected.

7. Comment summary: There is something left to be desired with regard to the contention that significant tumor data have been observed in mice. The summary of the draft document refers to a finding of a higher incidence of malignant tumors in mice for filtered diesel exhaust than for unfiltered exhaust. This finding as described in the draft is a perfect example of selective and incomplete reporting by the draft document. In 1989, an IARC working group pointed out that the incidence of lung tumors in the relevant historical controls could reach 32%; the referenced result removes any significance from the mouse studies. The TSD makes no mention of this. New results that are also not in the draft document have done away with the document's contention that significant tumor data have been observed in mice. The draft shows in several places that it upholds the notion that mice have shown significant tumor induction in diesel exhaust inhalation studies. (pp. 4-5, 8).

Response: The TSD has been revised to state that the results of carcinogenicity studies of diesel exhaust in mice are mixed. Assuming that the comment refers to the Heinrich et al. (1986) study, tumor incidence was higher in the filtered exhaust group than in the whole exhaust group (although no test of significance was reported), and the total (benign and malignant) tumor incidence for both exposure groups was significantly higher than that for controls. The usefulness of historical control data varies appreciably depending on the quality and study design of the studies they are derived from; such data should not be used to dismiss results from a well designed and conducted study. The TSD has also been revised to include mouse bioassay data by Heinrich et al. (1995) and Mauderly et al. (1996).

8. Comment summary: It is fair to say that so far, the induction of lung tumors by diesel exhaust has only been observed in rats. Most scientists having experience in this field are presently inclined to contemplate the lung tumors of rats by diesel exhaust, carbon black and titanium dioxide to be a rat-specific phenomenon of lung overload ("overload carcinogenesis") that does not occur in other rodents even when they are subject to long-term exposures that cause lung overload. Overload carcinogenesis is definitely not chemical carcinogenesis as observed with chemicals that react directly with DNA to give raise to mutations and cancer. To compare this rat phenomenon with lung cancer due to exposure to asbestos fibers is superficial "wish bias." Animal data show that asbestos fibers can trigger tumor induction at very low exposures, while overload carcinogenesis has never been observed when the lung burden was in a range where macrophage-mediated alveolar lung clearance was not impaired. Furthermore, unlike overload

carcinogenesis experimental fiber carcinogenesis in inhalation studies is not confined to rats. The document should address these current issues in a proper way. (p. 5)

Response: The current draft TSD Part B describes the studies by Heinrich et al. (1995) and Nikula et al. (1995) which compared rat lung tumor incidence rates after inhalation exposure to diesel exhaust, carbon black or TiO_2. The revised TSD (Part B, Chapter 7) also discusses the hypothesis that, in rats exposed to high levels of diesel exhaust by inhalation, particle concentrations exceed pulmonary clearance capacity and lead to chronic inflammation, which causes macrophage and/or neutrophil-induced oxidative DNA damage, resulting in both mutations, which may be mechanistically important in the induction of lung tumors, and cell proliferation, which may be mechanistically important to the promotion of lung tumors. However, Chapter 3 of Part B discusses bioavailability and metabolic activation of particle-associated organics, and Chapter 5 describes extraction under physiological conditions of mutagens from diesel exhaust. Chapter 5 also cites findings of increased lymphocyte DNA adducts in humans occupationally exposed to diesel exhaust and lung DNA adducts in rats after diesel exhaust exposure. Chapter 7 notes that the possibility that genotoxicity due to the PAH and nitroPAH content of diesel exhaust plays a role in the induction of lung tumors in rats at lower levels of diesel exhaust cannot be excluded.

The epidemiological studies discussed in the TSD provide a strong indication that cancer, not necessarily "overload carcinogenesis", associated with diesel exhaust has been observed in humans.

The new draft of the TSD does not make a comparison between asbestos and diesel exhaust exposures in animals. Staff could not locate such a comparison in the 1994 draft. Exposure to asbestos involves particles that are considerably different both chemically and physically than diesel exhaust particulate matter. Additionally, exposure to diesel exhaust involves both particles and a semivolatile phase. Therefore, making comparisons between asbestos and diesel exhaust exposure is problematic.

9. Comment summary: The draft document's conclusions show blatant disregard for scientifically relevant mechanistic aspects when extrapolating rat cancer study results to man. It is unfair to scare the public with lung cancer produced by diesel soot in rats by an obscure mechanism not yet seen in other species. Even innocuous substances like titanium dioxide, which served as a negative control in many toxicological investigations of the past, induce overload lung cancer in rats. At worst, diesel exhaust could be an undeterminable borderline carcinogen due to the proven genotoxicity of extracts of diesel soot particles. A chemical carcinogenesis mediated via reactivity with DNA and induction of mutations can only be theoretically postulated and would be merely hypothetical. There are no animal experiments showing anything else but overload carcinogenesis which, so far, was seen to occur only in rats. It is unlikely that evaluations of the rat studies render any useful information with regard to a human risk of lung cancer from diesel exhaust. (pp. 6, 14)

Response: There are potentially several mechanisms simultaneously contributing to the overall observed carcinogenicity associated with diesel exhaust. The genotoxicity of diesel exhaust particles and the organics adsorbed on them is well-documented.

Some of the tumors observed in rats might indeed be rat-specific. The TSD has been revised to include an expanded discussion of the uncertainties involved in the extrapolation of human cancer risk from rat lung tumor data.

The current draft describes the studies by Heinrich et al. (1995) and Nikula et al. (1995) which compared rat lung tumor incidence rates after inhalation exposure to diesel exhaust, carbon black or TiO_2. The revised TSD (Part B, Chapter,7) also discusses the hypothesis that, in rats exposed to high levels of diesel exhaust by inhalation, particle concentrations exceed pulmonary clearance capacity and lead to chronic inflammation, which causes macrophage and/or neutrophil-induced oxidative DNA damage, resulting in both mutations, which may be mechanistically important in the induction of lung tumors, and cell proliferation, which may be mechanistically important to the promotion of lung tumors. However, Chapter 3 of Part B discusses bioavailability and metabolic activation of particle-associated organics, and Chapter 5 describes extraction under physiological conditions of mutagens from diesel exhaust. Chapter 5 also cites findings of increased lymphocyte DNA adducts in humans occupationally exposed to diesel exhaust and lung DNA adducts in rats after diesel exhaust exposure.

The epidemiological studies discussed in the TSD provide a strong indication that cancer, not necessarily "overload carcinogenesis", associated with diesel exhaust has been observed in humans.

The rat bioassays evaluated in the TSD do not allow for direct examination of effects at low doses due to limitations in the power of the studies to detect low-incidence effects. Such limitations could greatly hinder or prevent the detection of tumors that may be due to the genotoxic components of diesel exhaust.

The cancer risk assessment for diesel exhaust presented in the TSD is not intended to "scare the public," and does not place undue emphasis on the lung cancer produced in rats. Although it includes rat data-based risk estimates, the TSD places greater emphasis on human data-based estimates. The TSD presents the risk assessment analyses in a fair and balanced manner. It states that the data do not allow for a definitive conclusion regarding the precise mechanisms involved in producing the observed lung cancer in rats. The human data are preferred by OEHHA staff. The rat data are viewed as reasonably consistent with and supportive of the epidemiology-based results. The rat data actually provide a somewhat lower estimate of the potential cancer risk than do the epidemiological data. From this perspective, the elucidation of the precise mechanisms involved in the rat carcinogenesis is not of primary importance.

The animal data have provided clear and consistent evidence of non-specific pulmonary inflammatory responses and other adverse effects in the alveolar region, in rats and guinea pigs exposed to diesel exhaust for long periods of time. These effects clearly begin at concentrations that are well below those associated with any overload phenomenon. (As defined in the TSD --

Part B, Chapter 4, "overload" is the point at which additional exposure concentrations do not correspond to increased clearance.) In addition, such effects are not expected to be species-specific since they involve very common, well-conserved mechanisms of action such as neutrophil-mediated inflammation or the formation of fenestrae in alveoli. The limited human data available indicate that there are immunologic effects in the upper airways that have not yet been reported in rats even at high doses. Therefore, other adverse pulmonary effects of inhaled diesel exhaust are reasonably expected to occur in humans as well as experimental animals.

10. Comment summary: The second paragraph of the "Conclusions" section (Section 1.5) looks like it was written in 1986. There is no doubt today that overload carcinogenesis is not related to the genotoxicity found with diesel soot extracts. Overload carcinogenesis is clearly an epigenetic process with no identifiable carcinogen to begin with. In this case, the existence of a no-effect threshold is seriously discussed and advocated by many competent scientists. (p. 6)

Response: Most of the paragraph referenced in the comment has been deleted. The issue of threshold is now discussed in a new section entitled "Sources of Uncertainty in Quantitative Risk Assessment," which has been added immediately before the conclusions section. The conclusion of the contested paragraph has been modified and is now presented there. It now reads, "The in vitro and in vivo genotoxicity of diesel exhaust suggests that a non-threshold mechanism for carcinogenesis may be involved. The Moolgavkar quantitative analyses of the rat cancer bioassay did not suggest there was a threshold for the carcinogenicity of diesel exhaust in the rat. ... at present, the limited evidence available does not allow a threshold for carcinogenesis to be identified."

There are potentially several mechanisms simultaneously contributing to the overall observed carcinogenicity associated with diesel exhaust. The genotoxicity of diesel exhaust particles and the organics adsorbed on them is well-documented. The epidemiological studies discussed in the TSD provide a strong indication that cancer, not necessarily "overload carcinogenesis", associated with diesel exhaust has been observed in humans. Nevertheless, the TSD reflects the fact that a possible threshold is seriously discussed by competent scientists. Chapter 6 of Part B has been revised to include a discussion of potential mechanisms of diesel exhaust-induced tumorigenesis. These mechanisms are also mentioned in the discussion of the uncertainties inherent in estimating human cancer risk from the rat lung tumor data in Chapter 7.

11. Comment summary: Regarding the third paragraph of the "Conclusions" (Section 1.5): Overload carcinogenesis cannot be treated like chemical carcinogenesis by molecular agents. And the models used were designed for chemical carcinogenesis. When mentioning the potential reasons for the disparities between the results for animals and humans, the draft document takes them for real and robust rather than artificial and hypothetical. At least, however, the document rightfully mentions the lack of knowledge of the appropriate way in which to calculate from rats to humans. The situation could be different for reliable epidemiological results. In the light of recent evidence (e.g., a report by Crump et al. that was submitted to the U.S EPA in 1991) that is ignored by the draft document, using the studies on the US railroad workers for a risk assessment is no less of an arbitrary conjecture than the extrapolations from rats. (pp. 6, 9-14)

Response: The beginning of the paragraph referenced by the comment was meant to be a straightforward summary of models and numerical values in the document. In the new draft TSD, this more simply presents numerical risk estimate values without reference to the extrapolation models. Discussions about overload-like phenomena and models for the rat data are elsewhere in the text. In this connection language has been added to the new draft TSD to emphasize that there is greater uncertainty in the range of risks cited for both humans and animals than is implied simply by the numerical values. The new draft summary chapter mentions overload in Sections 1.3.1 (Animal Tests) and 1.4.1 (Toxicokinetics).

Where the summary chapter mentions potential reasons for the disparities between the results for animal and human data, it conveys uncertainty (the sentence says the disparities "may be due to the predictions based on human data do appear to be more useful (because of less uncertainty of their applicability) than the predictions based on animal data.

The 1994 TSD did not cite the report of Crump et al. (1991b) because it had not been released until after the TSD was prepared, and there appeared to be unresolved contradictions between two of its principal results. As pointed out in Section 7.3 and Appendix E of the current draft TSD, the result in the Crump et al. report that cast the most doubt on the Garshick et al. (1988) result for railroad workers was due to an inappropriate calculation.

12. Comment summary: The fourth paragraph of the "Conclusions" (Part B, Section 1.5) is sensible (pp. 6-7)

Response: Comment noted.

13. Comment summary: The lung cancer statistics of the United States would not change by one iota if all diesel engines were banned. (p. 7)

Response: The new draft Part B (Section 7~6) presents a range of estimates of the number of lung cancer deaths that would be due to lifetime exposure to the average concentration of diesel exhaust to which Californians are exposed, based on new analyses of both rat and human data.

14. Comment summary: Reporting on the mouse studies by Pepelko and Peirano (1983), the draft document is somewhat open-ended with no bottom-line evaluation. To obtain a proper perspective, it may be sufficient to quote the authors. With regard to the results with Jackson A and Strong A mice, the authors pointed out that the protocol was merely suitable as a screening test using macroscopic adenoma counting, and made other points regarding the inconsistent results with Strong A mice. Based on these points, and going by the rules of statistical evaluation, there were no mixed results. This was just a negative study. The complex protocol of the inhalation study with Sencar mice on an interaction between diesel exhaust and initiators or promoters gave results that remain uncommented on in the draft document. The original paper reveals that this was a preliminary study, and 11 years later, there has been no follow-up. It would be legitimate for the document to conclude that the inhalation studies with mice by Pepelko and Peirano (1983) were essentially negative. (p. 8)

Response: The evidence for carcinogenicity of diesel exhaust in mice is not clearly positive or negative. Therefore, mouse tumor data (including the study by Pepelko and Peirano (1983)) were not used to derive human cancer risk estimates. Additionally, the study design would tend to reduce the sensitivity of the bioassay compared to a standard bioassay where exposure occurs for approximately the lifetime of the animal. This study demonstrated an elevated lung tumor incidence in female Strong A mice at the 6 mg/m 3 exposure level but not at the 12 mg/m^3 exposure. These results are properly described as being mixed. Additionally, diesel exhaust-exposed female SENCAR mice demonstrated an increased lung tumor incidence when compared to controls. Nothing in either the study design or conduct or the resulting data analysis justifies disregarding the positive tumor incidence data in this study. Thus, the TSD does not conclude that the inhalation studies with mice by Pepelko and Peirano (1983) were essentially negative.

15. Comment summary: The Takemoto et al. (1986) study deserves additional comments; it may have had an unusual experience with control groups. (pp. 8-9)

Response: The control groups in the Takemoto et al. (1986) study are not remarkable. Other reviewers of mouse diesel exhaust inhalation exposure studies (IARC, 1989; WHO, 1996) have not described any control group problems in this study.

16. Comment summary: Two of the three selected case-control studies are only briefly mentioned in the draft document. These are those of Benhamou et al. (1988) and Hayes et al. (1989). Behnamou et al. made no claim that their data were related to diesel exhaust inhalation; instead, they mentioned the presence of PAHs. Hayes et al. stated that they could not evaluate whether diesel or gasoline engine exposure was more strongly associated with the lung cancer risk found among workers in motor-exhaust related occupations. Thus, in view of the fact that no data on the drivers' actual exposure were acquired, the risk analysis remained rather inconclusive. (p. 11)

Response: The document's discussion (in Section 6.2.1.1 of Part B) of these two studies has been expanded in response to this comment. We note here, in regard to Behnamou et al. (1988), that PAHs are components of diesel exhaust, and, in regard to Hayes et al. (1989), that actual exposure measurements were not available for most case-control studies.

17. Comment summary: The draft document correctly reports the data obtained by Boffetta et al. (1988) from the first two years of the American Cancer Society's prospective mortality study with regard to mortality and diesel exhaust exposure. However, the draft document does not discuss the weak points of the study as presented by the authors. At least, the most serious bias should not be ignored; this was introduced because 92,038 members of the study population, i.e., 20% of the cohort, were excluded from the analysis due to lack of information on their diesel exposure. This is particularly important due to the fact that these members experienced a higher mortality -for all causes as well as for lung cancer than both the exposed and the unexposed group. A very conservative, but not unlikely, way of adjusting for this bias would be to assume that all people who did not report their diesel exposure, although they had been asked for it, were actually unexposed and should be added to the reference group. This may be justified because people who did not answer the question on whether they were exposed to diesel exhaust may

have felt they were not involved with diesel exhaust. This adjustment gives relative risks that are no longer significantly elevated. (pp. 11-12)

Response: In the Boffetta et al. (1988) study no evidence implies that those individuals who declined to answer the question about diesel exposure were actually unexposed. However, in this case, considering the group who did not report their exposure to diesel exhaust to be entirely unexposed is likely to have produced a downward bias in the estimate of the relative risk for exposed subjects, as pointed out in the study. This is noted in the TSD's review of the Boffetta et al. (1988) study (Part B, Section 6.2).

18. Comment summary: An important study by Crump et al. was submitted to the USEPA in 1991. It is difficult to understand why the California draft document simply ignores its existence. (pp. 12-14)

Response: The 1994 TSD did not cite the report of Crump et al. (1991b) because it had not been released until after the TSD was prepared, and there appeared to be unresolved contradictions between two of its principal results. As pointed out in Section 7.3 and Appendix E of the current draft TSD, the result in the Crump et al. report that cast the most doubt on the Garshick et al. (1988) result for railroad workers was due to an inappropriate calculation.

19. Comment summary: If we assume that the ambient diesel soot concentration is 5 $\mu g/m^3$, then the highest unit risk estimate presented in the document would indicate that 1 person out of 100 in the U.S. will be dying from omnipresent diesel exhaust. It is hard to understand that people believe in these fictitious numbers. (p. 14)

Response: The highest unit risk cited in the document is an upper confidence limit (UCL) for the calculation of risk and it does result in the very high prediction for the probability of death due to lung cancer at that concentration of diesel exhaust. Other sources, as reviewed in Chapter 7 of Part B, have determined similar UCLs for unit risk. The new version of that chapter contains the same value for the highest unit risk, but the statewide exposure concentration is reduced to 2.2 $\mu g/m^3$ in Part A. So the resulting prediction of the UCL for the lifetime probability of dying of lung cancer becomes approximately 1/200 for the California population and the maximum likelihood estimate becomes 1/300.

20. Comment summary: The document stretches diesel exhaust epidemiology beyond its limits. Even the most thoughtfully designed cohort study yields inconsistent results at relative risk values below 2.0 when tried for a dose-response relationship. This may be taken as an indication that there is no causal relationship that could yield a consistent dose-response curve. (p. 14)

Response: The TSD now includes a meta-analysis to more reliably assess the epidemiologic data. The meta-analysis in Appendix D of Part B provides a thorough analysis of the epidemiologic data on diesel exhaust and lung cancer. It also provides some support for a dose-response relationship.

21. Comment summary: Regarding the document's quantitative risk assessment (Chapter 7): The U.S. EPA has abstained from any further use of the data of the 1988 Garshick study for risk assessments because of the inconsistent, or non-existing dose-response relationship as revealed by Crump and others. Although a direct human risk assessment from epidemiological. data would be most desirable, there are no adequate data available even from the most heralded of the pertinent epidemiological studies. The most probable explanation would be that there is no causal relationship between diesel soot inhalation and lung cancer. However, due to the statistical nature of epidemiological studies, the absence of a very small effect can never be proven. (Additional comments dated October 11, 1994, pp. 1-2)

Response: In the Review Draft of their "Health Assessment Document for Diesel Emissions, December, 1994," which was published several months after this comment was sent, the U.S. EPA cited the Garshick et al. (1988) cohort study in their weight-of-evidence assessment of the carcinogenicity of diesel exhaust as Category B1, probable human carcinogen (Section 11.2). The U.S. EPA did not use any human data in the dose-response for their quantitative risk assessment (Section 12.4.2.1). They did not use the results of the Garshick et al. (1988) cohort study in part because of the Crump et al. (1991) report did not find a pattern that was consistent with an association between diesel exhaust exposure and lung cancer (Section 11.4). The U.S. EPA document was published before the documentation of a problem with a set of principal analyses of the Crump et al. report.

Support for the finding of a carcinogenic effect of diesel exhaust also comes from the meta-analysis in Appendix D of Part B.

22. Comment summary: The document's quantitative risk assessment has no adequate description of its dose computations. For instance, between page 7-3 and 7-12 there are at least 8 pertinent references which cannot be found in the reference list. Among them is a report (Hattis and Silver, 1992) whose source the commenter could not get through the common literature services. The commenter had to scan relevant publications in order to find out that the publication was an unpublished report to the Laborers' Health and Safety Funds. The report is repeatedly invoked in the draft document. Furthermore, no direct references are made to the Weibull and Moolgavkar models, and the derivation of the internal doses to be used in these models remains obscure. (Additional comments, p. 2)

Response: In response to this comment, appropriate adjustments have been made to the reference list. Note that the "doses" used in the Weibull and Moolgavkar models (cumulative lung deposition and lung burden) are explicitly defined in Sections 7.2.1, 7.2.2, 7.2.3, and again, for the purposes of scaling results to humans, in Section 7.2.6 of Part B. Additionally, specific references to both the Weibull and Moolgavkar models are given in Section 7.2.5. The internal doses used in the calculations using Weibull and Moolgavkar models are explained in Section 7.2.3, and the software used to apply the models is cited in Section 7.2.5.

23. Comment summary: The second sentence of Section 7.3.3, in the risk assessment from an epidemiological study, states that, in each of the two models considered, the dose has a different definition, "as in the analysis of the rat results." This, however, is correct only in case of the first

model, which characterizes dose as "cumulative atmospheric exposure to diesel exhaust." That value is proportional to the exposure concentration as used for the rat study assessment. The other model characterizes dose as cumulative exposure based on lung burden; in the analogous rat analysis (Section 7.2.2), dose is rather imprecisely defined, but the definition becomes clear by reading Table 7-2. The logistic regression for the tumor prevalence by Mauderly allowed for two potential dose parameters, viz. the atmospheric exposure concentration and the actual lung burden at the end of the lifetime exposure. Apparently, the same dose parameters were used to derive the parameters of the Weibull and Moolgavkar model, notwithstanding the fact that the lifetime lung burden is not suitable as a dose parameter in these models.

In equations (1) to (3) in Section 7.2.2 , it is clear that the dose D which is actually a dose rate (like mg/day) must not be a time integral. In the opening paragraph of that Section, it is (almost) correctly stated that "each model requires a constant exposure level or dose rate as input."

The evaluation procedure of the Garshick epidemiology data did not use the lung burden at the end of the lifetime exposure, although Figure 7-4 gives this incorrect impression. The ordinate values in this graph do not represent milligrams of lung burden, but "AUC" area under the curve, i.e. the time integral of the lung burden in milligram-years. This time-integral would not be a suitable parameter for the two chemical carcinogenesis models. (Additional comments, pp. 2-3)

Response: The role of lung burden for the animal models has been clarified in the document. In the animal models lung burden is treated like concentration and its average value over the course of the experiment is entered into the TOX_RISK program. So the result obtains the risk for exposure to (average) lung burden over the course of the experiment. This consideration applies to the two time-to-tumor models used for the rats. This is analogous to the way human exposure to lung burden was treated in the 1994 draft TSD. Human exposure to varying lung burden is not considered in the new draft TSD. The commenter correctly points out that Equations 7-1 through 7-3 are correctly considered to be for a dose rate that is constant over the course of the experiment.

The analysis of human data based on variable lung burden and the resulting figure do not appear in the revised TSD.

24. Comment summary: As used in the TSD, chemical carcinogenesis models are not adequate for insoluble particles. Constant exposure concentration of insoluble particles is not a suitable substitute for the constant dose rate required by the chemical carcinogenesis models. Overload carcinogenesis is not the same thing as chemical carcinogenesis (which has an easily defined dose modified only in its effectiveness by the particular biochemical mechanism causing the tumor formation).

In view of this principal problem, the problems of deriving theoretical expressions for the patterns of lung burdens in relation to the exposure concentration are almost trivial and of secondary order. However, using an irrelevant retention kinetics model out of a 1969 textbook (Figure 7-1) is certainly not a convincing approach. (Additional comments, p. 3)

Response: As pointed out in Section 7.2 of Part B. the risk model using atmospheric exposure assumes constant concentration and the risk model using lung burden assumes that lung burden is constant over the course of the experiment. The average atmospheric concentration was essentially constant from week to week, implying that the dose rate of particles into the lung was also constant from week to week. The lung burden, however, which is the particular concern of the commenter, did not reach steady state at the higher exposures but continued to increase over the course of the experiment, an overload situation. Nevertheless, the risk model for lung burden uses, as a working approximation, a constant value equal to the average of actual measured values over the course of the experiment, because no computer program which could follow the variable time-course of exposure and also take account the very nonlinear risk response was available to us. The assumption of constant concentration, which also essentially implies a constant hazard rate, may produce only a very approximate result, but that result is based entirely on average measured values of lung burden and not on any toxicokinetic model. In the absence of more definitive evidence on mechanisms of the carcinogenesis, which may or may not involve only the insoluble portion of the particle, this calculation appears to give a useful estimate of risk.

The classic compartmental retention model from the text by Atkins (1969) applies only to the calculation required to scale the lung burden to the unit of atmospheric concentration for risk predictions at the low concentrations of a few micrograms per cubic meter of atmospheric environmental exposure. Such a simple linear model is the approximate limiting form for a host of complex nonlinear models and may be expected to apply to these kinetics.

25. Comment summary: A model without a physiological base is simply not suitable for general applications. Equation 17 on page 7-16 is deplorable in that it is a one-compartment model with a heuristic Michaelis-Menten kinetics approach. This model ignores overload and leads, similarly to the classical linear retention model, to a maximum lung burden in a steady state. This Smith model will not describe the build-up of lymph node deposits which are measured in most of the recent inhalation studies of tumor induction by overload carcinogenesis and may play an indicator role as shown in a manuscript this commenter submitted for consideration. (Additional comments, p. 3)

Response: The previous response to comment showed where a limited pharmacological model served a purpose. This comment represents another such case. The fact that the Smith model has only one compartment makes it subject to valid criticism. However, the commenter is incorrect about the concentration always reaching steady state. For parameters such that EVX >R/Km, the solution to the differential equation for lung burden becomes asymptotic to (EVX -R/Km) t , which increases without limit as time increases. This property is reminiscent of a property of the commenter's latest POCK model. The Smith model does not describe the lymph node deposits, which could play an indicator role. Possible improvements on the Smith model have been considered but the current analysis does not need such a model because of the removal of shopworkers from the analysis of the Garshick et al. (1988) cohort. The remaining workers are expected to have a sufficiently low exposure that their lung burden is approximately proportional to exposure.

26. Comment summary: A multi-compartmental kinetics model for the alveolar region is needed. The central problem is devising an appropriate overload carcinogenesis model. If this is solved, one faces the practically insurmountable task of coming up with a credible extrapolation model from rat to man. That a model may be quite useful for rats, but not work for hamsters. or other animals (let alone man) has not been considered as a source of uncertainty of the risk assessments in the draft document, because there was little physiological relevance in all of the retention models used so far in the context of risk assessment approaches. (Additional comments, pp. 3-4)

Response: This comment, in stating a "central problem," presumes that "overload carcinogenesis" has been established as the operating mechanism for diesel exhaust. OEHHA staff do not agree. We do agree, however, that the extrapolation from animal data to human cancer involves considerable uncertainty. Although the draft TSD may not have discussed rat-to-hamster extrapolation in particular, interspecies extrapolation is considered as a source of uncertainty in the risk assessment.

A number of particle retention models have been recently modified and improved by Dr. Stöber (the commenter) and others. A discussion of these and other retention models is included in Part B of the TSD, in chapter 3. However, the advent of more sophisticated models for the estimation of physiological fate of inhaled diesel particles does not address the uncertainty surrounding the mechanism of carcinogenesis. These models are useful if it is assumed that the only mechanism for carcinogenesis is subject to a threshold due to particle overload. However, the available data do not support such an assumption.

27. Comment summary: Even if the POCK model were used in the TSD's assessment of human risk from diesel exhaust inhalation, the TSD's present approach results in highly hypothetical risks that are taken for real by the general public although the numerous assumptions and uncertainties remove the assessment process from the realm of sound science. In view of the established facts that the rat tumors are not caused by chemical carcinogenesis and that there are no tangible epidemiological results indicating diesel exhaust to cause lung cancer, the hypothetical risks in case of overload carcinogenesis must be based on a dose-response relationship that is different from the proportionality between low dose and low risk as it is used in case of chemical carcinogenesis. (Additional comments, p. 4)

Response: What the comment describes as established facts (that the rat tumors are not caused by chemical carcinogenesis and that there are no tangible epidemiological results indicating diesel exhaust to cause lung cancer) are actually not established. The commenter has not documented the claimed response to the TSD by the general public. Note that the TSD sets forth numerous caveats for its estimates. Although low-dose cancer risk assessment is subject to much uncertainty, the TSD's estimates are the product of sound risk assessment practice. The available scientific data are sufficient to support the risk estimates provided in the document.

Comments of the Western States Petroleum Association

1. Comment summary: This commenter endorses the "Joint Comments on the California Air Resources Board's Proposed Identification of Diesel Exhaust as a Toxic Air Contaminant", dated October 14, 1994. (Letter from Jeff Sickenger, Environmental Issues Coordinator, dated October 14, 1994, p. 1)

Response:Comment noted.

2. Comment summary: This commenter appreciates the effort undertaken by ARB and OEHHA in developing the draft TSD and its acknowledgment of many uncertainties associated with the data. (Oct. 14 Letter, p. 1)

Response: Comment noted.

3. Comment summary: There is a substantial body of scientific evidence that has not been adequately addressed in the TSD which suggests that the preliminary risk estimates are significantly flawed. Inconsistencies between conclusions drawn in the draft Part A and B documents and other scientific evidence must be reconciled before the draft documents can serve as a basis for further analysis. (Oct. 14 Letter, p. 1)

Response: The staffs of ARB and OEHHA have considered the comments on the 1994 draft TSD and have extensively updated and revised the TSD. After the release of the 1994 draft, the staffs conducted public and scientific workshops to gather further information. In addition, OEHHA and ARB have considered more recent comprehensive reviews released by the U.S. EPA and the Health Effects Institute. The staffs have revised the draft report to incorporate all the available data and comments. As currently written, the document can serve as a basis for a decision on whether or not to identify diesel exhaust as a toxic air contaminant.

4. Comment summary: While the authors of the health risk assessment document have done a good job of identifying many of the assumptions and uncertainties in the analysis, technical flaws remain that invalidate the document's numerical conclusions. (Appendix by Tony Cox, dated October 10, 1994, p. 1)

Response: Please see responses to specific comments, below.

5. Comment summary: The data selected for the animal risk assessment do not fairly represent all relevant information. Data that do not support the hypothesis of a positive dose-response relation between diesel exhaust and lung tumors were ignored in the analysis. This biases risk estimates upward.

Part B calls Mauderly et al.'s 1987 experiment on rats "the most appropriate animal study for calculating risks." However, it has not been shown that rat lung tumors are a biologically relevant model for human lung tumors in response to diesel exhaust. Nor has it been shown that the rat data are more relevant than mouse data or hamster data for predicting human risk. Biological

relevance should be discussed and data from multiple species should be considered unless there is compelling evidence that only the rat data are useful for predicting human risks.

Studies should not be selected or excluded based on their conclusions, rather than on their intrinsic soundness. A statement on p. 7-2 of Part B could suggest that only mouse studies showing positive lung tumor responses were selected for evaluation. This would be biased data selection.

Studies should not be excluded because they contain little useful quantitative dose response data if they provide useful qualitative evidence on whether realistic concentrations of diesel exhaust cause any increase in lung tumor risk. For example, the study of Pepelko and Peirano (1983) should be included, even if it does not lead to a "straight-forward dose-relationship."

Concentrating on a single species (the rat) does not provide a full. description of the human risk to be expected based on animal data. A judgment of how "like" other species humans are in their health responses to diesel exhaust must be made to extrapolate human risks from animal ones. Assuming 100% relevance of rat data and 0% relevance of all other species seems unrealistic, and in any case should be discussed and justified explicitly. The probability that the risk to humans is as high as the rat data predict is less than 1 if the mouse or hamster data may turn out to provide a better prediction than the rat data of human responses. (An approach for down-weighting the probability predicted by a source with uncertain predictive reliability is suggested by an article in the Journal of the American Statistical Association.)

To overcome selection biases and to present a full and balanced view of relevant data, OEHHA could use meta-analysis of multiple studies and species. This would overcome the non-representative nature of predictions based on a single study. At a minimum, attention should be given to meta-analysis questions such as whether the selected study is generally consistent with evidence from other species and studies, including ones that provide useful, valid information but which might not contain enough information individually to be appropriate for risk assessment in isolation. (Cox, pp. 1-4)

Response: The carcinogenicity of diesel exhaust in rats has been established (see Section 6.1 of Part B). Section 7.2 of Part B contributes to the TSD's risk assessment; its purpose is to provide animal data-based risk estimates that may be useful to the risk manager seeking to protect public health. The methods used there (dataset selection, analysis, and presentation of results) are in accordance with standard, widely-accepted risk assessment practice. Mechanisms of carcinogenesis and sensitivity to carcinogens may differ among species. The assumption that humans are at least as sensitive to a carcinogen as the most sensitive animal species tested (in this case, the rat) is health protective. Both the U.S. EPA and IARC have concluded based on the total weight of evidence that diesel exhaust is a probable human carcinogen. This conclusion is based on the animal, human, and ancillary data. A risk estimate of zero, even if based on a negative study, would be contrary to this weight of evidence judgment. The 1994 draft focused on the best studies for which there was the most definitive data to calculate risks. Rats have been the most thoroughly studied of all experimental animals with regard to chronic diesel exhaust exposure. The Mauderly et al. (1987) study had the only data that included individual time-to-

tumor formation for a full lifespan. This study therefore was selected as the most appropriate animal study for use in risk estimation on the basis of its "intrinsic soundness." The current draft TSD includes analyses for all the data on rats that had sufficient exposure and more than one exposed group of animals; so the resulting range of risks should give a fair picture of the expected range of upper confidence limits (UCLs) for unit risk in such rats.

Hamsters have not developed tumors in response to diesel exhaust, yet hamsters treated with diethylnitrosamine or benzo[a]pyrene (but not exposed to diesel exhaust) unexpectedly showed only low incidences of respiratory tract tumors (Heinrich et al., 1986). Low pulmonary sensitivity to genotoxic carcinogens could potentially account for the lack of carcinogenic response to diesel exhaust in hamsters. Although investigators have conducted three studies of diesel exhaust inhalation and lung cancer in hamsters (these are described in the TSD), OEHHA staff do not generally consider the hamster to be a useful model for qualitative or quantitative risk assessment of potential human lung carcinogens. In reporting their negative findings with diesel exhaust, Heinrich et al. (1986) pointed out that "contrary to the rat," hamsters have "failed to develop lung tumors ... after inhalation of high concentrations of pure BaP (benzo(a)pyrene] or even cigarette smoke, a well known human carcinogen." Ten years later, the International Agency for Research on Cancer (1996) specifically addressed the relative strengths and weaknesses of the hamster model for different tumor types. IARC, too, noted that there have been no reports of lung tumor development in hamsters due to inhalation of benzo(a)pyrene or cigarette smoke. IARC stated that even with radionuclides it is difficult to induce lung tumors in hamsters, except with intratracheal instillation of polonium-210. Nickel and silica were both negative in hamsters upon inhalation or instillation. Instillations of glass fibers and asbestos have yielded mixed results. The insensitivity of the model indicates that hamster data should not be considered valid predictors of human lung cancer risk. Thus the TSD does not present quantitative risk estimates based on the hamster data.

Data from mouse studies are limited in quantity, and have thus far been mixed with regard to determining carcinogenic potential of diesel exhaust.

The study by Pepelko and Peirano (1983), which examined a wide array of cancer and non-cancer effects, is discussed under non-cancer health effects (Chapter 4). The carcinogenic investigations in hamsters were hampered by a epidemic that greatly reduced the number of survivors. The mice were exposed for only 15 months, rather than a full lifetime. For these reasons, the equivocal results of this study are not emphasized in the TSD.

A "meta-analysis" of the animal studies might provide an interesting quantitative picture of the overall risk to rodents. If such a study were available and of high quality, it would be discussed in the document as a supplement to the present approach of the document to discuss the results of the laboratory studies and their implications. The OEHHA staff's view is that the present approach is adequate, in part because the risk estimate range is based only partly on the animal studies and because the results from the animal studies underpredict the results from the human studies.

6. Comment summary: Both the animal and the human risk models selected by OEHHA use dose metrics that have not been validated or critically evaluated as predictors of risk. Independent of the statistical risk model used, extrapolations of low-dose risks based on these dose metrics are speculative and tend to over-estimate the true risks at low doses if overwhelming of lung clearance capacity plays a key role in the causation of lung tumors by diesel exhaust.

The draft risk assessment assumes that equal cumulative exposures (measured either as ppm-weeks of exposure or as mg-weeks of elemental carbon in the lungs) create equal risks in rats, independent of how the total amount of exposure is allocated over time. This assumption is incorrect and will exaggerate the risks predicted at low doses if overwhelming of lung clearance capacity is an important part of the mechanism of diesel exhaust-induced carcinogenesis. Data are consistent with the hypothesis that overwhelming occurs at high concentrations.

The lung clearance model used to calculate lung burden assumes linear kinetics. This assumption is not warranted without further discussion, especially if overburdening of the lung with particulate matter at high, long-sustained concentrations (a nonlinear phenomenon) is a key mechanism in the etiology of rat lung tumors in the Mauderly et al. experiments. Thus, "dosimetric equivalencies" calculated by OEHHA are conjectures based on an unvalidated two-compartment model that is probably incorrect.

The validity of the selected dose metrics should be tested and critically assessed. Meta-analysis of past studies or new stop-exposure experiments and cell proliferation assays could help assess the validity of the selected dose metrics. As an interim measure, biomathematical models of saturation of normal lung clearance might suggest more predictive dose metrics. (Cox, p. 4)

Response: The TSD's assumption of cumulative exposure in ppm-weeks as a dose metric in the TSD is plausible and quite customary in risk models for animals and humans. The assumption of cumulative exposure to lung burden in mg-weeks as a dose metric is not customary but is plausible given the data from the Mauderly et al. (1987) study that show an overload effect on lung clearance and a sharp rise in cancer incidence with the rise in lung burden with increasing duration of exposure. The comment does not state the basis for the claim that an overload of lung clearance capacity invalidates the use of these dose metrics, which progressively increase with duration of exposure. The comment does not suggest an alternative dose metric that could be evaluated for its validity.

The lung clearance model for the rat studies is linear, as the comment notes, and is therefore valid only in the linear range of the relationship of risk to cumulative exposure. So, as the revised text of Section 7.2 now emphasizes, this model is used only to make the conversion from risk per lung burden to risk per atmospheric concentration of 1 $\mu g/m^3$, and at this low concentration it is quite valid.

The comment does not explain how a "meta-analysis" would help to test the choice of dose metric. As to the suggestion to use "biomathematical models of saturation of normal lung clearance," each model still needs to specify the dose metric that is being predicted and does not say how that is to be done differently. The approach in the TSD is to use actual measurements of

lung burden, thus avoiding lung burden modeling except in one of the final steps (converting the risk per lung burden to risk per atmospheric concentration at low values of concentration).

7. Comment summary: The statistical models selected to analyze the rat data have not been validated. They contain simplifications and approximations that may make them inapplicable to the rat data. They do not account for potentially relevant biological effects (such as overwhelming of the lung's clearance capacity, which OEHHA's pharmacokinetics model assumes does not occur despite evidence to the contrary) and cell proliferation caused by damage to lung tissue from diesel particulates. These omissions tend to bias model-based low-dose risk estimates upward. The draft selects two parametric families of dose-response models for the rat data. Neither model form is known to describe the diesel exhaust dose-response relation for rat lung tumors. Neither family of models considers pharmacokinetics or cell proliferation triggered by tissue damage or cytotoxicity. If these factors are important, then it seems unlikely that the administered dose-response relation will have one of the two selected forms.

The draft suggests that the Moolgavkar model "takes cell proliferation into account" in a way that is relevant for diesel exhaust-induced lung tumorigenesis. This is not true. The selected Moolgavkar model form does not model compensating cell proliferation or regenerative hyperplasia following cell injury in the lung. Yet, these pharmacodynamic processes may drive diesel exhaust carcinogenesis. Modulating the Moolgavkar model's parameters over time to represent pharmacodynamics associated with exposure to diesel exhaust requires a separate biomathematical model. The exponential time function in the approximate Moolgavkar model should not be expected to describe the cell proliferation involved in diesel exhaust tumorigenesis.

Both selected model forms are based on approximations that treat tumors as rare events. Errors created by this approximation should be quantified, since the rat tumor incidence rates exceed 10%. Preliminary calculations using nonlinear regression to fit both exact and approximate multistage models to the Mauderly et al. data indicate that the approximate model gives risk estimates that are more than twice as great as those from the exact model for most (but not all) dose levels.

Neither model accounts for age-specific transition rates and size of the initiated population when dosing begins. Human and rat median ages at death are assumed to be comparable, but ages at the start of dosing have not been equated across species. The age-specific form of the multistage model has not been used.

OEHHA's risk predictions contain unquantified errors and biases due to the selection of specific model forms without considering a full set of alternatives. The descriptive adequacy of each selected model form could be tested, e.g., by embedding it in a wider set of models and carrying out an analysis of deviance, but this has not been done. Uncertainty about model form has also not been considered in preparing the "95% UCLs" in the report, which therefore do not indicate (and may significantly understate) the true range of uncertainty about risks. Computer-intensive techniques such as model averaging could be used to reduce model selection biases and to improve the predictive ability of OEHHA's risk models.

Some rat tumors exhibit nonlinear, threshold-like dose-response behavior for some chemical carcinogens. It is also known that specific mechanisms of rat carcinogenesis at these sites do not apply to humans, e.g., due to anatomical, metabolic, and other physiological differences. These biological lessons suggest that empirical validation must be performed before applying simple risk models to rat tumor data and expecting (or betting policy decisions on the assumption) that the results usefully predict human health risks. The models selected by OEHHA have not been empirically validated.

The selected model forms are too restrictive to guarantee that the best-fitting member of each family provides a useful approximation to the true dose-response curve. By contrast, some recent statistical techniques use "generalized representations" to guarantee that the best-fitting model in a class will be close to the true model when sufficiently many data points are given. The selected model forms do not have this property. In the absence of empirical validation, statistical hypothesis testing, or specific biomathematical modeling of the pharmacodynamics appropriate for diesel exhaust induction of rat lung tumors, it is plausible that the true dose-response relation may fall significantly outside the two classes considered. This is consistent with the TSD's observation that the maximum likelihood member of each class has a latency period of zero for development of a detectable tumor, which is biologically unrealistic. (Cox, pp. 4-7)

Response: As pointed out in Section 7.2 of the 1994 draft TSD, the risk models used for the rat data of Mauderly (1987) are standard models from the TOX_RISK computer program. The comment does not specify the kind of validation that would make them acceptable to the commenter. An "empirical validation" of the modeling results would entail the use of animal studies on an extremely large scale in order to detect low incidences of tumors. Typically, risk models are not validated empirically this way for practical reasons. Incurring the costs of such a large test would be of questionable utility.

The statistical models selected contain simplifications and approximations but are the most applicable to the rat data of available models. The models provided an adequate fit of the data, as shown in Table 7.4 of the revised TSD. Pharmacokinetic modeling to describe effects such as clearance capacity on lung burden is not needed because actual lung burden is used. The Weibull model does not specifically take into account cell proliferation as such, but the Moolgavkar model did take into account very approximately a relevant aspect of cell proliferation, an aspect that is dependent on cumulative exposure and allows for a potential threshold but found that none was present. Although this approach does not specifically include the effect of tissue damage or cytotoxicity, the dose dependence of the general cell proliferation effect may be expected to approximate the specific effect of the damage. The comment does not say why the exponential time function in the approximated Moolgavkar model would be inapplicable. These considerations counter the possibility that "omissions" may bias low-dose risk estimates upward.

A 10% tumor rate does suggest that the approximate Moolgavkar model used in the TSD on the assumption of tumors being rare events may not give precise results. Thus, the comment's suggestion that the TSD's predictions may be twice as high as predictions given by the more exact form of model indicates that the exact form of the model would be needed if that calculation were the determining calculation for unit risks. Specific data on cell proliferation

rates would generally be important in the effective use of the exact model. However, the absence of such data does not suggest that the bias is upward. When cell proliferation data were incorporated in the Toxic Air Contaminant Program TSD for formaldehyde, the risk estimate generally increased, thus suggesting that a bias due to omitting the proliferation effect was downward.

Use of the age-specific form of the multistage model (Crump and Howe, 1984) might also improve the accuracy of the calculation. A computer program for such a model in the highly non-linear case of the Mauderly et al. (1987) rats does not appear to be available. The idea of embedding each model used in a wider set of models has the potential to provide a quantitative description of uncertainty about the choices of model. The approach of the TSD provides a more qualitative description of these uncertainties. As in the previous paragraphs, the limited result is taken to suffice for modeling these data.

The comment does not document the assertion that some rat tumors exhibit nonlinear, threshold-like dose-response behavior for some chemical carcinogens nor that specific mechanisms of rat carcinogenesis at these sites do not apply to humans, e.g., due to anatomical, metabolic, and other physiological differences. Further, the comment does not explain what is meant by an empirical validation that must be performed before applying results to humans. The kind of mechanistic studies that would be useful to support the critical extrapolation from rats to humans are simply not available and are difficult to do.

The comment does not specify how generalized representations could be used to incorporate the best mechanistic information about carcinogenesis to develop estimates of risk. The use of such models would be a departure from established practices in risk assessment.

With regard to latency, the four different analyses of the Mauderly et al. (1987) data did give the results of zero latent period, within the precision of bioassay data. The definition of latency in these models is the time between carcinogenesis and detection of the tumor. For this definition, there is no biological implausibility because the actual latency could have been a few months, a time that might not have been detectable with this bioassay and analysis.

OEHHA staff believe that the selected model forms provide useful approximations to the true dose-response curve. Furthermore, we are not aware of other available models with more existing validation for this specific effect than the standard models selected.

8. Comment summary: The maximum-likelihood parameter estimation methods used to fit the selected statistical risk models to rat data contain limitations that have not been discussed by OEHHA. They do not fairly represent the full range of plausible parameter values and risk estimates based on the data.

Within each of the two model families it considers (Weibull multistage and simplified Moolgavkar), OEHHA's risk assessment selects the one specific model that appears to be most consistent with the data, in that no other model in the same family would ascribe a higher likelihood to the observed data. The estimated low-dose slope and upper confidence limit are

based on this "maximum-likelihood" model. Choosing one model in a family and ignoring the rest - even those that provide equally or almost equally high likelihoods for the data - fails to give a complete picture of the plausible range of risks. For example, the most probable model (obtained by conditioning prior information on the observed data) in general differs from the maximum-likelihood model. Its predictions are ignored when only the maximum-likelihood model is considered.

The maximum-likelihood model may give quantitatively inaccurate risk estimates, especially if several distinct curves in the same model family provide essentially equally good fits to the observed data but different risk predictions outside the observed range. For example, fitting different quantal multistage models to the Mauderly et al. data on p. 7-25 of Part B via nonlinear least squares regression shows that three specific models fit the data approximately equally well. All three explain approximately 99.9% of the variance in the data points. Their values (-0.002, 0.0044, 0) for q, may all be about equally plausible, with the single "best" value (using the minimum mean squared error criterion) being 0. (Negative values of q_1 are allowed since cytotoxic effects that reduce the average number of cells at risk of malignant transformation cannot be excluded.) For comparison, the MLE estimate of described in footnote f, page 7-27 of OEHHA's draft report may be calculated to be 0.0035, well within this range of values.

Choosing q, = 0 as the only value to consider and calculating 95% UCLs for the other coefficients would clearly not represent the full range of plausible risk models and would yield a misleadingly narrow range of risk predictions. Yet this is analogous to OEHHA's procedure, except that quantal data and the minimum mean squared error (MSE) criterion have been used to fit parameter values instead of time-to-tumor data (not provided in detail in the draft report) and the maximum likelihood (MLE) criterion. None of several model forms provides a fit that is so much better than the others as to justify disregarding them. By restricting attention to the subset of models with q2 0 and q, > 0 and ignoring essentially equally plausible models with q, = 0 and q_2 > 0 (or with q, < 0 and q_2 > 0) OEHHA's draft report may have focused on an inappropriately narrow (and artificially high) range of values for q_l. (Cox, pp. 7-8)

Response: Although the maximum-likelihood estimate (MLE) plays an essential role in determining the 95% UCL of the unit risk, it is the UCL that is the health protective result of the risk calculation. The comment's idea of presenting a fuller account of the parameter variation possible with only slightly lower values of the likelihood function would give a more mathematically complete result but would unnecessarily complicate the TSD's presentation. For the TSD's purposes, it is fair to follow standard risk assessment practice and focus on the likely case of low-dose linearity, for which the present approach gives an estimate for 95% UCL. In this standard context, there is no need to explore hypotheses that are squared or cubic in exposure, rather than linear.

The presentation of 95% upper confidence limits (UCLs) for unit risks, as in the TSD, represents standard practice for cancer risk assessments. In addition the current draft of the TSD gives the maximum likelihood estimate (MLE) referred to in the comment. The size of the upper portion of the confidence interval, the difference between the 95% confidence limits and the MLE, gives an indication of the uncertainty of the cancer potency estimate. In some cases, the MLE is unstable.

In those cases, the expectation value of the distribution can be a useful descriptor to provide for the central tendency of the estimate of unit risk. Including negative values in this distribution, as the comment suggests, would not alter the expectation value and does not sound useful, because the probability that diesel exhaust reduces the cancer risk of an exposed population is a proposition that may be assumed to have negligible probability. -The idea of assuming the unit risk equals zero or less and determining an MLE value for the coefficient that is quadratic in cumulative exposure may be mathematically complete, but is currently outside the realm of practicality.

9. Comment summary: It is not clear why the q_1^* value reported in Table 7-2 of Part B is smaller than 0.0035, the MLE value calculated from footnote f. (Cox, p. 8)

Response: The MLE value calculated from footnote f is actually

$$4.8 \times 2.97 \times 10^{-14} \times 131.7^{5.377} = 0.0356 \ (mg/m^3)^{-1} = 0.0000356 \ (\mu g/m^3)^{-1}$$

not 0.0035, as stated in the comment. The value of the UCL, q_1^*, was given in Table 7.2 of the 1994 draft TSD as 3.2×10^{-5} , the units of which were meant to be stated as $(\mu g/m^3)^{-1}$ though the table appears to label the units as $(mg/m^3)^{-1}$. To obtain the lifetime UCL value, footnote d specifies multiplying by an intermittency factor of 4.8, as in the above equation for the MLE. The resulting value of UCL is 1.5×10^{-4} $(\mu g/m^3)^{-1}$, about 4 times greater than the above MLE value of 3.6×10^{-5}, in the same units.

10. Comment summary: The maximum-likelihood methods used to quantify uncertainties and confidence bounds on the parameters do not adequately represent the true uncertainties in the analysis. The methods referred to in the OEHHA risk assessment have limitations which are not discussed there. The upper confidence limits (UCLs) are based on an asymptotic result that has poor convergence properties for many real data sets. Its accuracy for the Mauderly et al. data set is unknown. It may not apply to the Weibull multistage model with non-negative coefficients (since the underlying necessary conditions for convergence have not been shown to hold). In practice, this approach does not provide a good approximation of the distribution observed for small bioassays when Monte Carlo simulation is used. Thus, even if the underlying models were known to be correct, the 95% UCLs reported by OEHHA are probably inaccurate. To obtain accurate confidence limits, computationally intensive methods such as Monte Carlo simulation should be used. The numbers presented in the TSD as 95% UCLs differ by unknown amounts from the correct 95% UCLs.

The estimated UCLs are implicitly based on the (false) assumption that the selected model form is known to be correct. If several different model forms are considered, then the assumptions needed to obtain the asymptotic UCL estimates may not hold. Thus, when model uncertainty is taken into account, the claimed 95% UCLs lack theoretical justification even as asymptotic approximations. To the extent that they ignore other plausible models that give lower risk estimates, they might well correspond to bounds that have a 99% or greater Bayesian probability of exceeding the true values.

Regarding a statement on page 7-4 of the draft risk assessment, the hypothesis that presence of lung tumors does not affect the hazard rate for mortality should be formally tested before it is used. More generally, the most appropriate techniques for analyzing the Mauderly et al. rat data are the methods of censored survival data analysis, with interim deaths and sacrifices being treated as censoring events. These appropriate models and methods (e.g., quasi-likelihood methods) have not been used. (Cox, pp. 8-9)

Response: In support of the assertion that the standard asymptotic approximation used to obtain the UCLs in the TSD may be inaccurate, the comment cites an article by Poitier and Hoel (1983). That article points out that large errors can be made in characterizing the UCL if the wrong rigid model is chosen. However, if a flexible model is used, and in that article a flexible (linear-quadratic) model is used, then the largest discrepancy given between the asymptotic approximation and the Monte Carlo simulation was an underestimate of the UCL by a ratio of approximately $10^{-.28}/10^{-.53} = 1.8$. That example was for only 150 animals, and the article points out that the discrepancy is less for more animals. Mauderly et al. used approximately 900 animals, thus tending to reduce such discrepancy. The revised TSD mentions this source of uncertainty.

By its nature, risk assessment involves uncertainties. "Model uncertainty". was once treated by quoting results from a wide range of model types, many of which were considered improbable. The results did not appear useful and this approach has not appeared in recent risk assessments by Cal/EPA or U.S. EPA. Instead it has been found most useful to use the linearized multistage model as the basic model for animal data and to incorporate other data-driven models in the analysis. That is the approach used in this TSD. The models used in the TSD involve different sets of assumptions, yet yield quite similar results. However, it is unreasonable to assume that any risk assessment model is exactly accurate. The models used in the TSD are the most plausible available. They are both generally accepted and widely used. Although the models may not be known to be correct, the UCLs presented are correct for the models. Section 7.2 has been revised to add that other models that fit the data about as well could give very different results, and that these models are not considered to be as plausible as the models used.

No distinction between incidental and fatal tumors is actually made in the TOX_RISK program. The following sentence has been added immediately preceding the sentence referred to on page 7-4 of the 1994 TSD, to make clear that a survival analysis was performed: "The form of the likelihood function for the survival analysis takes account of time of death with lung tumor as well as censoring of such observations due to any deaths in which lung tumors were not detected."

11. Comment summary: The linear relative risk model selected to analyze the human data is not valid. It contains inappropriate assumptions and restrictions and ignores errors in estimated doses for individuals that bias its risk estimates upward and invalidate its numerical conclusions.

The TSD uses a linear relative risk model to relate the relative risk of lung tumors in humans to cumulative exposure to diesel exhaust. This model produces predicted response probabilities greater than 1 at sufficiently high doses. Perhaps recognizing this limitation, the risk assessment

"assumes that each of these linear models (actually, the same model with different dose metrics) is adequate at the occupational atmospheric concentrations which are well below those at which tumors are elevated in the rat bioassays." (Part B, page 7-13). An approach with greater potential biological justification is to assume a linear proportional hazards model of a particular form. Since the two models converge at sufficiently small values of the independent variable (dose), the OEHHA human model is an approximation to the linear proportional hazards model. Since the TSD uses a multistage model to extrapolate human risks from rat data, it would be more consistent to fit a multistage model to the human data rather than to arbitrarily assume a linear relative risk model, which is a special case of the multistage model.

OEHHA assumes that the slope of the relative risk model is constant, independent of dose. This hypothesis should be tested (e.g., by fitting a multistage polynomial model to the data and then testing whether the coefficients of terms of order greater than 1 differ significantly from 0). The regression residuals in Figure 7-6 (p. 7-42) suggest that the constant-slope assumption may be inappropriate for the Garshick data. Nonlinear relative risk models fit the data better.

Measurement errors have been omitted from the risk assessment model for humans. The linear relative risk assessment model is an incorrect model for the Garshick data, because estimates of dose were reconstructed from uncertain approximations (not shown in this model). A more realistic model (the commenter suggests one) would incorporate the error in estimated exposure.

OEHHA's estimate of the slope of the relative risk curve is biased upwards by failure to use an appropriate errors-in-variables model, which shifts the conditional frequency distribution of exposures among workers who develop tumors compared to the conditional distribution of exposures among workers who do not develop tumors (assuming that exposure and risk are positively associated). Ignoring measurement error ignores this shift, thus biasing risk estimates upward. In any group of workers having identical estimated exposures, tumors are more likely to occur among those workers whose true exposures are higher than the estimated level than among workers whose true exposures are lower than the estimated level. (At zero exposure, however, there may be no room for estimation error, in which case no bias occurs.) In summary, the validity of the human risk estimates based on the Garshick et al. data has been compromised by OEHHA's failure to model errors in estimates of exposure. The consequences are: (a) The estimated slope of the dose-response curve is confounded with the variance of the exposure estimation error. Until this problem is corrected, the current risk estimates based on human data should not be used. (b) At all dose levels that increase risk, risk estimates will tend to be biased upward. The strength of the bias tends to increase with the variance (and thus probably also with the level) of exposure.

Ignored measurement error alone can explain an apparently positive relation between exposure duration and risk. Workers who have been exposed for more years may accumulate larger variances of their true cumulative exposures around their estimated cumulative exposures. The high end of this distribution of true exposures will tend to contribute disproportionately many observed responses for the same level of estimated exposure. A positive association between duration of exposure to a constant average exposure level and estimated risk may be created (or explained) by the increase in error variance of estimated exposure as exposure duration increases.

Failure to correct risk estimates for this phenomenon creates unquantified biases in OEHHA's risk estimates.

OEHHA has ignored interindividual heterogeneity in dose-response functions in specifying its selected (linear relative risk) model. Fitting a model with homogeneous parameters to the data when a mixture distribution model describes the real situation creates two problems: (1) The risk model will not give correct predictions on average. The observed response rates from any sensitive, early individual responders will be incorrectly attributed to the average individuals in the population. Thus, an unquantified portion of the estimated positive relation between exposure and response may be due to ignored heterogeneity. (2) The risk model will not predict the right thing. It attempts to quantify the risk at any dose level, rather than quantifying the population frequency distribution of individual risks at that dose level. Yet it is the change in the population frequency distribution of individual risks created by different risk management decisions that should be quantified to inform decision-makers about the probable health consequences of different decisions. The draft risk assessment could be made more valuable (and perhaps biases could be removed) by testing whether a mixture distribution model describes the Garshick data. (Cox, pp. 9-13)

Response: This response maintains that the linear relative risk model is valid for the purposes of this quantitative risk assessment. The assumptions and restrictions made for purposes of simplicity of analysis do not appear to result in any bias that would compromise the estimates made.

In regard to the need for the use of a proportional hazards model instead, the commenter has not provided an analysis based on the suggestions presented in the comment, but has indicated that using the suggested methods would make little difference in the dose range of concern. Two simple comparisons show that the linear relative risk model is a good approximation to the proportional hazards model in the range of the human data. In this range the predicted response probabilities are far less than 1. Both comparisons use a lifetime concentration of 100 $\mu g/m^3$, a very high value even for occupational exposure, in order to assess the fullest extent of any difference. The first comparison uses a unit risk of 3.00×10^{-4} $(\text{lifetime-}\mu g/m^3)^{-1}$, the bottom of the range of human-based risk estimates. Using the relative risk model, direct multiplication of unit risk and concentration then gives a lifetime risk of 3.00×10^{-2}. Using the proportional hazards model, evaluation of the exponential gives $1 - \exp(-3.00 \times 10^{2}) = 2.96 \times 10^{-2}$. The other comparison uses a unit risk of 2.00×10^{-3}, the top of the range of human-based risk estimates. Here the relative risk model gives a gives a lifetime risk of 2.00×10^{-1}, and the proportional hazards model gives $1 - \exp(-2.00 \times 10^{-1}) = 1.81 \times 10^{-1}$. The use of unit risk at the bottom of the range clearly results in a negligible difference while the use of the unit risk at the top of the range results in a difference (10%) that is not substantial in this context. Thus, as the comment goes on to point out, the OEHHA human model is a good approximation to the linear proportional hazards model and the OEHHA approach gives results that are similar to the commenter's preferred approach in the dose range of concern.

In regard to the assertion that it would be more consistent to fit a multistage model, the Garshick et al. study reports relative risks for only four categories of exposure duration. So it does not

seem to be prudent to estimate more than one coefficient to describe the trend. Even when estimating just two coefficients, the variance of the estimates becomes large, resulting in lack of statistical significance.

In regard to the TSD not considering errors in measurement, the comment offers and intuitive argument for upward bias but does not supply any calculation of what the magnitude of that effect might be. For the simple linear regression in the 1994 draft, an approximate estimate of the effect on the slope calculation is readily made. A standard text (such as that cited in the comment or W.L. Hayes, Statistics, 4th ed., Holt Reinhart and Winston, 1988, p. 583) derives a formula showing that the measurement errors bias the estimate of true slope downward via a factor of 1/(l + variance ratio). The variance ratio is of variance in measurement errors to the variance of the true measurements. If the measurement errors are simply considered to be uniformly distributed errors of the duration of exposure appearing in the linear regression, then this ratio is less than 1%. Considering the measurement errors to include the uncertainty and variability of exposure concentration and misclassification of exposure duration, the bias is unlikely to exceed 10%. Even in the simple case under discussion, it is not clear how the errors of categorizing the exposure variable should be characterized. A normal approximation to the categorized variables does not appear to be appropriate. The problem would lead to even more complexity in the analyses in the current draft TSD, analyses which start with the individual data. While the comment speaks of the estimated slope of the dose-response curve being confounded with the variance of the exposure estimation error, the comment does not characterize the magnitude of any likely effect. OEHHA staff, then, do not agree that the realism of the present approach needs to be improved or that something needs to be corrected before the current risk estimates based on human data can be used.

In regard to the analyses in the TSD not considering heterogeneity of the population, the comment is correct in pointing out that the present results for unit risk do not furnish information about differing sensitivities in the population. Such information could lead to more precise and even more accurate results. However, there are some drawbacks to the suggestion. The use of a mixture model would add a substantial degree of complexity to the analysis. We do not know if this approach would yield reliable information about the differing sensitivities of the components of the population. The comment does not provide any help on how the distributional form of the result might be successfully implemented. It appears that more information would be needed on the mechanism of action (to understand how human responses may differ) and the range of susceptibility of humans to diesel exhaust exposure. Modeling such issues would likely involve more assumptions that could not be verified. Distributional information has not been available for any previous TAC. We do not know how essential the additional information is to risk managers. In sum the suggestion is very interesting, and in theory perhaps useful, but it appears that the more traditional approach of the TSD to unit risk is adequate for the purposes of the TSD.

12. Comment summary: A nonlinear relative risk model fits the data used by OEHHA better than the selected linear relative risk model. It is more consistent with the data and with the hypothesis that cancer risk is disproportionately high at very high doses. The nonlinear relative risk model leads to an upper 95% confidence limit of zero on the low-dose slope of the dose-response curve.

OEHHA's hypothesis of linear relative risk should be rejected in favor of the alternative hypotheses that relative risk is an increasing function. Alternative nonlinear regressions with models fit to data in the TSD explain more of the variance in the data. A model of the form $q_0 + q_1x^3$ is a better model; it explains 68.5% of the variance, compared to 33.6% by OEHHA's $q_0 + q_1x$ model. Using OEHHA's model in place of the better-fitting model for relative risk greatly increases the low-dose risk estimates.

If OEHHA's regression procedure in Table 7-8 is applied with the dose variable transformed to x^2, x^3, and so forth, then all measures of goodness of fit show that the model for x^3 fits the data in the table 7-8 better than does the linear relative risk model.

The commenter has verified most of the numbers presented in Table 7-8, but it appears that the reported value of R^2 is too small.

OEHHA's approach to model selection for rat data involved predicting risk based on the best-fitting (maximum-likelihood) member of each model class considered. The same approach applied to the human data would require ignoring the linear relative risk model and using a nonlinear (e.g., cubic) relative risk model instead. Within the cubic relative risk model form, the 95% UCL on unit risk (defined as the slope of the dose-response function at the origin) would be zero.

The possibility of nonlinear dose-response relations should not be ignored in presenting quantitative risk estimates for diesel exhaust. Both the “expectation value” and the confidence limits presented in Table 7-8 assume without justification that the linear relative risk model is correct and ignore better-fitting nonlinear relative risk models.

To improve the risk assessment based on Garshick's epidemiological data, alternatives to the linear relative risk model (e.g., Weibull multistage or Moolgavkar) should be used to predict absolute risk as a function of total cumulative exposure (including background).

The dramatic increase in risk between the third and fourth data points in Table 7-8 suggests that a threshold (or other highly nonlinear) effect may be present, so that the same dose-response function may not describe both high-dose and low-dose data. This observation is consistent with the biological hypothesis that saturation effects play a key role in elevating risk at sufficiently high, long exposures. The current (unvalidated) lung clearance model denies this possibility by assuming linear kinetics. (Cox, pp. 13-15)

Response: The revised text in Section 7.2 now discusses more specifically the possible alternative mathematical forms. In regard to nonlinear relative risk model fitting better, there are two general reasons for using the linear form of calculation summarized in Table 7-8 of the 1994 draft TSD and in Table 7-10 of the revised draft. (1) The multistage theory predicts linearity at low exposure when background tumor rates are not zero. (2) The relative risks provided by Garshick et al. (1988) are subject to considerable uncertainty. Also Appendix E of the current draft TSD now shows results for several analyses that differ from the Garshick et al. result in that they do not have the sharp rise in the estimate of relative risk in the highest exposed group, and

they have more uniform standard errors across the exposed groups. In some of these analyses the risk for the highest exposure group actually declines. These analyses include Armitage-Doll models, which are akin to the models that the comments give as examples for alternatives and which returned essentially linear results. Thus, even though the comment presents mathematical forms that fit the published relative risks better than the linear model in the 1994 draft TSD, the use of the simple linear form in Table 7-8 of that draft and in other analyses in the new draft TSD is not only justified but also prudent with the actual Garshick et al. data.

The comment that the R^2 in Table 7-8 of the 1994 TSD 0.338 appears to be too low is inconsistent with the comment's presentation of the linear term explaining 33.6% of the variance in the data. Those are essentially the same numbers.

As noted above in response to Comment 6, the trend of the human data used in the risk assessment is not statistically distinguishable from linearity. In the new draft TSD, the figure that displays the trend shows the large error bars on the points, in agreement with the results of the formal statistical test. Although tests of other models might show somewhat better fits, a simple linear relationship appears to be the most reasonable choice at present for humans, with no real indication of sublinearity.

In regard to analyzing the human data by the same approach to model selection used for the rat data, the assertion that this approach would result in a non-linear (e.g. cubic) relative risk model with no linear component appears to be incorrect. The approach to model selection for the rat data was essentially that of the linearized multistage model. Consistent with the theoretical constraint and contrary to the suggestion to use only a cubic term to characterize the exposure-response relationship, the linearized multistage approach guarantees a positive linear component of the UCL of the risk function. I

In regard to the suggestion to use alternative models, Appendix E of the current TSD uses with individual data the Armitage-Doll model, which is a form of multistage model. Exposure above background is used in this model. Also in Appendix E, a linear relative risk model uses total cumulative exposure including background.

In regard to the sharp rise in the relative risk for the fourth and highest exposed category possibly indicating a threshold or other highly non-linear effects, see the beginning paragraph of this response. Also, the lung clearance model used for the workers in the 1994 analysis was nonlinear and specifically does allow for saturation. This clearance model is not used in the current draft TSD because shopworkers, who were the only railroad workers to have had a high enough exposure to need such a model, are no longer considered in the main analyses using such exposure information.

13. Comment summary: The human data have not been adequately adjusted for age, for smoking behavior, and for exposure to environmental contaminants other than diesel exhaust. An unknown proportion of the risk attributed to diesel exhaust may in fact be due to other sources. For example, if both lung cancer risk and cumulative exposure to diesel exhaust increase with

age, then a spurious positive association will exist between them that is not adequately corrected for in Table 7-8.

Separate risk estimates are not presented for smokers and nonsmokers in the Garshick et al. study, although it is claimed that the effect of smoking on relative risk may be small. It is not clear how large this effect really is, nor how to adjust the relative risk calculations to apply to other populations with different smoking compositions.

No consideration has been given to attribution of risk among multiple causal factors in OEHHA's draft report. If diesel exhaust interacts with other factors to increase lung tumor risk, then attributing all of the risk to diesel exhaust artificially inflates estimates of the risks "due to" diesel exhaust.

Age and exposure history appear to be confounded in OEHHA's risk assessment. No age adjustment has been made in converting from relative to absolute risks. Although Garshick apparently controlled for age in his analysis, an analogous age-specific correction appears to be missing from this part of OEHHA's quantitative risk assessment. Thus, an unknown proportion of the cancer risk attributed by OEHHA to diesel exposure may in reality be due to a spurious correlation between cumulative exposure to diesel exhaust and incidence of lung tumors, simply because older workers may tend to have more of both.

Risks attributed to diesel exposure may in fact have been due to other, co-occurring environmental hazards. This possibility, acknowledged in OEHHA's draft in conjunction with failure to control for confounding factors in many of the studies surveyed, undermines OEHHA's conclusion that it appears that the evidence is sufficient that diesel exhaust contributes to human lung cancer. Unless and until the possibility can be ruled out (or at least made implausible) that smoking, age, and exposures to other occupational and/or environmental carcinogens fully account for the relatively weak associations between diesel exhaust exposure and human lung tumors, the suggested causal interpretation cannot be established with sufficient confidence to provide a useful, reliable basis for policy decisions. (Cox, pp. 15-16)

Response: The human data were adjusted indirectly for age in the proportional hazards model of Garshick et al. (1988). (1) Baseline incidence was a continuous (year-to-year) function of time. (2) An indicator variable for the relative risk (RR) of each 5-year interval of age-at-the-start-of-study (relative to the risk for the youngest age interval) entered the model multiplicatively. (3) An indicator variable for the RR of each exposure-duration interval (relative to the lowest exposure-duration interval) entered the model multiplicatively.

With regard to risk estimates for smokers and non-smokers, see Section 7.2 of this document's Part B or the Garshick et al. (1987a) case-control study for a basic account. Based on the findings reported there, this document's dose-response model assumes no interaction of any covariate with exposure. The effect of smoking enters multiplicatively only through the baseline incidence in the model described above.

With regard to age adjustment to that of the general population as well as with regard to adjustment for different smoking habits, the entire factor multiplying the exposure term of the model takes this into account. This approach is appropriate in so far as these effects are multiplicative, independent of exposure, as is assumed here on the basis of the available evidence. Thus, the possible confounding of age and exposure history when converting from relative to absolute risk does not appear to be realized.

The comment mentions the possibility that risks attributed to diesel exposure may have been due to other co-occurring environmental hazards. Although it is difficult to see how such explanations could be ruled out, the design and analyses of the Garshick et al. studies makes them implausible. The meta-analysis now included in this document bolsters the argument against alternative causes. Since the alternative-cause hypothesis is implausible, the comment's objection to using the TSD's findings for policy decisions is not valid.

14. Comment summary: When relevant statistical and biological uncertainties are taken into account, the OEHHA draft risk assessment has failed to show that there is a certainty or a strong likelihood of any excess risk to humans due to low levels of exposure to diesel exhaust. Additional information should be considered and more realistic quantifications of uncertainties about risks should be prepared before making risk management decisions. The current risk assessment does not contain enough useful information to justify expensive control actions.

Key uncertainties and sensitivities have been identified qualitatively and discussed well in the current draft Part B. However, they have not been treated quantitatively. It would be valuable to present numerical ranges for how the risk estimates would change as choices of data sets, risk model forms, and estimated risk model parameter values are varied over their full ranges of plausible values.

The regression output on page 7-34 of the risk assessment may create a misleading impression about the magnitude of health benefits to be expected from controlling exposure to diesel exhaust. A lower confidence limit of zero would more fairly indicate the true uncertainty about the health benefits, since these could well be zero (or negligible, as suggested in the discussion of the assumption of linearity on page 7-17). The assumptions of the risk models in the risk assessment have not been validated, and identified sources of bias have not been corrected for. The existence of a cancer hazard at low doses remains to be established. Focusing (without supporting evidence) on a set of assumptions that presupposes such a hazard and that then predicts significant risks at realistic concentrations based on it, in the absence of empirical data supporting this conclusion, could mislead decision-makers into believing that significant health benefits would result from more tightly controlling diesel exhaust exposures.

OEHHA's discussion of uncertainties on pages 7-17 through 7-19 is overly optimistic in several places. For example, it states (Point 1) that the four data points of risk used against cumulative exposure of the cohort "do not allow a test of departure of the exposure-response relationship from linearity." In fact, the four data points can be used to test (and reject the null hypothesis of linearity against alternatives such as that the exposure-response relation is quadratic or cubic. The assumption that half of the shop workers were exposed to very high levels of diesel exhaust

and the rest to zero (i.e., background levels; Point 6) is an inadequate substitute for mixture distribution modeling of population exposures.

The list of uncertainties is also incomplete. As discussed in comments above, (1) Errors in exposure estimates are ignored; (2) Interindividual variability in dose-response relations is ignored; (3) Model uncertainties (in the model forms considered and in the best-fitting member of each model family) are ignored; and (4) Parameter estimation uncertainties are incorrectly characterized by assuming that the correct model is known.

The risk extrapolations in the TSD, both within rats and from rats to humans, are not known to be sound or useful. The fact that the dose metrics used do not allow successful risk extrapolation even from rats to hamsters may cast doubt on their predictive validity for non-rodent species. The TSD presents no empirical evidence that builds confidence in the soundness and predictive power of the selected risk extrapolation procedures. Therefore, risk extrapolations based on its rat models must be regarded as speculative. Confidence in OEHHA's model-based conclusions must be considered low.

Whether the current risk assessment is good enough to support high quality, well-informed decisions, despite its uncertainties, depends on whether the expected increase in the value of risk predictions (i.e., the expected improvement in decisions) from better modeling outweighs the costs of improving and/or validating the current models. It would be useful to address this topic explicitly in the TSD, so that decision makers can be well-informed about whether to accept the current risk assessment or to pay for better information.

Choosing a specific risk estimate in the absence of theoretical or empirical validation of its supporting models is equivalent, from a decision-theoretic perspective, to choosing one of many possible values at random: it does not provide an adequate basis for decision-making. Such a basis could be provided by displaying the full uncertainty distribution for a risk estimate, as well as sensitivity analysis information (e.g., "tornado diagrams") showing which uncertainties could most affect the estimated risk. These steps have not been taken in the current draft TSD, however. Thus, compared to the usual standards of professional decision analysis, OEHHA's current risk assessment draft report does not contain appropriate information displays presenting risks and uncertainties in a way that would enable decision makers to make rational, well-informed risk management decisions. (Cox, pp. 16-18)

Response: The TSD now presents a range of risk estimates. Additional information has been added to the document, including a meta-analysis of the epidemiological studies (Appendix D), quantitative exposure-response assessments using the Garshick (1987a) case-control study and using the Garshick et al. (1988) cohort study with shop workers excluded (Section 7.3), an analysis of the original data of the Garshick et al. (1987) cohort study (Appendix E), and computation of unit risks for several additional rat studies (Section 7.2). This additional information gives a strong indication of excess risk to humans and does not point to a threshold. OEHHA staff have endeavored to ensure that the TSD contains sufficient information for consideration by the risk manager to make informed decisions. Nevertheless, the document's main purpose is to support the proposed identification of diesel exhaust as a toxic air

contaminant. No benefits analysis is included because no specific risk reduction measure is proposed.

The revised TSD contains much new quantification of uncertainties. OEHHA staff are concerned about adding further complex analyses to the report because they would probably be of only of marginal interest to risk managers. Tornado diagrams, for example, would add to the comprehensiveness of the document but do not seem likely to be very helpful in risk management. Furthermore, the effort to prepare such diagrams would be considerable. We expect that risk management activities will be best carried on based on the more traditional presentation of the TSD. The revised Part B appears to have enough information to allow the Air Resources Board to pair it with the population exposure information in Part A for use by the risk managers. This process, as it has in the past, should enable decision-makers to make rational, well-informed risk management decisions.

The comment's suggested analysis that would help risk managers decide whether the expected increase in the value of risk predictions from an improved approach outweighs the cost of the making the improvement is interesting but appears to be beyond the scope of current law and would require a level of effort that may be infeasible.

The validity and usefulness of the regression output on p. 7-34 is argued in the response to Comment #12. A lower confidence limit on the slope could be zero, but the document cites the most reasonable results directly from calculations. The risk models used are standard and appear to be applicable. No significant source of bias of the analysis has been identified in the comment. Assumptions cannot be validated, or they would no longer be assumptions. Our intent in choosing assumptions is to use those that are most reasonable, sometimes with a central value, sometimes with values chosen to indicate a range. Assumptions are clearly identified.

The description in the TSD of the uncertainty listed in the comment as number (1) has been modified to include the point in the comment. The uncertainties suggested for discussion have also been included in the TSD. The issue of shop worker exposure has been avoided in the new draft by excluding shop workers from the analyses.

Risk extrapolations are typically uncertain and imprecise, but they are useful in estimating the magnitude of risks in the absence of complete data. OEHHA staff do not generally consider the hamster to be a useful model for qualitative or quantitative risk assessment of potential human lung carcinogens. In reporting their negative findings with diesel exhaust Heinrich et al. (1986) pointed out that "contrary to the rat," hamsters have "failed to develop lung tumors ... after inhalation of high concentrations of pure BaP (benzo(a)pyrene or even cigarette smoke, a well known human carcinogen." Ten years later, the International Agency for Research on Cancer (1996) specifically addressed the relative strengths and weaknesses of the hamster model for different tumor types. IARC, too, noted that there have been no reports of lung tumor development in hamsters due to inhalation of benzo(a)pyrene or cigarette smoke. IARC stated that even with radionuclides it is difficult to induce lung tumors in hamsters, except with intratracheal instillation of polonium-210. Nickel and silica were both negative in hamsters upon inhalation or instillation. Instillations of glass fibers and asbestos have yielded mixed results. The

insensitivity of the model indicates that hamster data should not be considered valid predictors of human lung cancer risk. Potential uncertainties about the soundness and predictive power of the extrapolations from animals suggests that one should place more of a focus on the human data-based risk predictions. Still, OEHHA has not chosen to present only a specific risk estimate, but rather has specified a whole range of unit risks.

15. Comment summary: This commenter's Oct. 14 submittal indicated the commenter's intent to review the basis for the non-cancer health effects levels (reference concentrations, or RfCs) proposed in the draft Part B. A preliminary review by the commenter indicates some shortcomings in the proposed (U.S. EPA)approach which should be considered. The following outlines the commenter's initial concerns:

Toxicological data may not support inclusion of a safety factor to account for interspecies sensitivity. The current U.S. EPA RfC includes a safety factor or 3 to account for uncertainty in interspecies variability. Dr. Donald Dungworth has commented to ARB that rats are considered more sensitive than humans for the endpoint used to establish the no observed adverse effect level. In view of that, the proposed uncertainty factor is not necessary. OEHHA should review Dr. Dungworth's assessment and take appropriate action.

Here the draft Part B does not consider available occupational health studies. The commenter's preliminary review identifies several previous or ongoing studies of carbon black workers that should be reviewed. If these studies can support the development of an RfC for diesel exhaust, that RfC could be used directly, or as a check against the RfC derived from rat data. OEHHA should review the available human data and contact investigators from ongoing epidemiological studies to determine if an RfC can be developed from the new data. (Letter from Jeff Sickenger, Environmental Issues Coordinator, dated November 30, 1994, pp. 1-2)

Response: Dr. Dungworth, before the Air Resources Board on September 14, 1994, stated: "Now there are not comparable studies as yet that I think are good enough to report of ... comparing the macrophage particle interaction in the human with the macrophage particle interaction in the rat." Macrophage activity is the endpoint used to establish the no observed adverse effect level. Therefore, Dr. Dungworth did not claim that rats are considered more sensitive than humans for this endpoint. In fact, data are not presently available that would allow direct comparison of human and rat sensitivities to non-cancer effects of diesel exhaust. Furthermore, a number of studies have shown adverse health effects in humans exposed to diesel exhaust that have not been reported in the rat, such as induction of asthma and various immune system reactions (Diaz-Sanchez et al., 1994; Takenaka et al., 1995; Wade and Newman, 1993). Thus, OEHHA staff find it appropriate to maintain an uncertainty factor for interspecies differences.

16. Comment summary: Differences between U.S. EPA and OEHHA on the unit risk factor for diesel particulate are significant and must be resolved. Apparently using the same health research database, OEHHA and U.S. EPA have calculated different unit risk factors for diesel exhaust. The carcinogenic unit risk factor adopted by OEHHA is 3×10^{-4} $(\mu g/m^3)^{-1}$ whereas the factor adopted by U.S. EPA is 1.7×10^{-5} $(\mu g/m^3)^{-1}$. The difference is significant and needs to be resolved. At a minimum, this difference should be acknowledged as part of a characterization of

the range of uncertainty in estimating exposure to diesel exhaust and the health risk posed by that exposure. This commenter strongly recommends a formal uncertainty analysis. Uncertainty analysis is important, given the wide range of estimated exposure an d risk and the very different policy implications of the different ends of that range.

More complete characterization of uncertainty and its implications is needed. Significant uncertainties are present throughout OEHHA's risk assessment. These include the above-mentioned differences in carcinogenic unit risk factor. Important uncertainties should be more fully acknowledged, the accompanying exposure and risk uncertainty range identified, and policy and decision implications discussed. Where significant sources of uncertainty are identified, additional research should be identified and conducted. The results of such research should be analyzed prior to listing of diesel exhaust as a toxic air contaminant. (Appendix, "Review of CARB Diesel Exhaust Exposure Assessment," by Environ, November 1994, pp. II-2, II-12 - II-17, II-23 - II-25, III-2, III-3)

Response: Throughout the preparation of the current draft of this document, OEHHA staff have consulted with U.S. EPA staff to discuss approaches to health risk assessment of diesel exhaust, to share findings, and to harmonize as much of our work as was feasible given our differing scheduling, internal and external review processes, statutory and regulatory frameworks, and resources. We expect that the range of risk estimates presented here by OEHHA and the range presented by the U.S. EPA will be similar. However, as of this writing, a new published U.S. EPA risk assessment report was not available. Thus, our document refers to the range of risk estimates in the U.S. EPA's 1994 draft report. In 1994 the U.S. EPA actually proposed to recommend 3.4 x 10^{-5} $(\mu g/m^3)^{-1}$, the geometric mean of their report's range, as the unit risk for continuous lifetime exposure.

This TSD acknowledges the differences between its recommended risk estimates and those of U.S. EPA. In so doing, it contributes to the characterization of the uncertainty in estimating the magnitude of health risk posed by exposure to diesel exhaust. The TSD does not present a formal uncertainty analysis, however. OEHHA staff understand that the communication of uncertainty in risk assessments is important. The current draft TSD represents a substantial improvement in this area over-the previous draft. New text and analyses in the current draft address sources of uncertainty more completely than before. Nevertheless, a Toxic Air Contaminants Program TSD is not a place for complete discussion of decision theory or policy implications of uncertainty. The basic aim of this TSD is to provide information sufficient to support a decision on whether to identify diesel exhaust as a toxic air contaminant.

There are significant sources of uncertainty in the risk assessment. Ideas for useful additional research can be identified, yet additional research need not be conducted prior to action on the proposal to list diesel exhaust as a toxic air contaminant. Diesel exhaust and its health effects have been studied extensively, and the TSD represents a synthesis of the large body of research. Although additional research would add to our understanding of diesel exhaust and associated health effects, and could reduce uncertainty in risk assessment, the available data are sufficient to support identification of diesel exhaust as a toxic air contaminant.

17. Comment summary: Significant reductions in estimated exposure and health risk are warranted. Correction for several factors will significantly reduce the exposure and health risk calculated by ARB and OEHHA. This includes a factor of 18 reduction for using U.S. EPA's unit risk factor instead of OEHHA's unit risk factor. The combined effect of these factors is about a 100-fold reduction in risk. Accounting for additional emissions reductions due to the increased phasing in of motor vehicle control measures, the risk in the year 2000 could be a factor of up to 200 less than given in the TSD. The U.S. EPA's Mobile Source-Related Air Toxics Study for 1995 calculated a risk that is a factor of about 60 less than the ARB/OEHHA value. At a minimum, a risk uncertainty range should be calculated and presented to decision makers, along with an analysis of the policy implications of uncertainty. (Environ, pp. II-26 - II-27, III-3)

Response: With the current revisions of Cal/EPA's and U.S. EPA's diesel exhaust risk assessment documents, and the provision of a range of risk estimates based upon animal and epidemiological findings by both agencies, it is expected that the differences between the agencies will have markedly diminished. Several of the factors mentioned in the comment relate to exposure. The Air Resources Board will consider future reductions in diesel exhaust emissions in any risk management decisions it makes regarding diesel exhaust.