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April 30, 1998

Dr. C. W. Jameson
National Toxicology Program
Report on Carcinogens
MD EC-14
P.O. Box 12233
Research Triangle Park, NC 27709

Re: Review of Diesel Particulates for
Potential Listing in the NTP's Report
on Carcinogens (Ninth Edition)

Dear Dr. Jameson:

On behalf of the Engine Manufacturers Association ("EMA"), we hereby submit the enclosed materials for consideration in connection with the National Toxicology Program ("NTP") review of whether "diesel particulates" should be listed in the NTP's Report on Carcinogens, Ninth Edition (the "9th Report") as a substance reasonably anticipated to be a human carcinogen.

EMA is the trade association that represents worldwide manufacturers of engines for all applications other than passenger cars and aircraft. Included among the many products manufactured by the more than 30 major corporations that comprise EMA's membership are a full array of diesel-fueled engines.

Through the efforts of EMA members, working in conjunction with federal and state agencies, dramatic engine design improvements and emissions reductions have been achieved. An

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especially relevant example of these advancements is that emissions of particulate matter from diesel engines have been reduced by 90% over the past decade.

Given the substantial improvements that industry has made in emissions reductions through advanced engine technology and reformulated fuels, the potential listing of "diesel particulates" in the 9th Report is a matter of vital importance to EMA and its members. EMA's members and consultants have substantial experience relating to the pending reviews of the potential health effects of diesel particulates, and have commented extensively on the draft health risk assessments for "diesel exhaust" that California's Office of Environmental Health Hazard Assessment ("OEHHA") and the U.S. Environmental Protection Agency ("EPA") have proposed.

With that in mind, EPA submits the following points for your consideration along with the enclosed materials. These points have been developed in response to opinions expressed by those active in recent debates on this topic, and are submitted to explain more fully the position of EMA on these extremely important issues.

1. Any Specific Listing For "Diesel Particulates" Must Be Specifically Justified

In considering a listing for "diesel particulates," a critical initial question to answer is why diesel particulates deserve classification separate from other fossil-fuel and renewable bio-fuel combustion products. Combustion soot from gasoline, heating oil, coal, charcoal, tobacco smoke, wood and cooking is ubiquitous throughout the United States. Unless and until it can be explained

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why the combustion product "diesel particulates" is markedly different from other combustion products, a listing singling out "diesel particulates" cannot be justified.

In addition, reviewers should fully and fairly inform the public of the true composition of the combustion products at issue to avoid fostering unwarranted alarm regarding diesel particulates. Thus, the NTP should note that: (i) ambient concentrations of diesel particulate (assessed through PM_{10} measurements) are less than 1/25th of the current NAAQS for PM_{10} ; (ii) the hydrocarbon fraction of diesel exhaust is only 7 parts per million of diesel exhaust; (iii) the PM fraction (even for pre-1991 diesel engines) is only 60 parts per million of diesel exhaust, and of that PM fraction the PAH content ranges from units to hundreds of parts per million; (iv) overall, the PAH content of whole undiluted diesel exhaust is below 0.01 part per million; (v) for the $1.5 \mu\text{g}/\text{m}^3$ diesel exhaust particulate concentrations to which most individuals are exposed, the concentrations of PAHs are less than $0.0001 \mu\text{g}/\text{m}^3$; and (vi) for an individual breathing 20m^3 per day, the daily PAH intake is approximately $0.002 \mu\text{g}/\text{m}^3$, an intake that is far below even typical background intake levels of PAHs which range from 2 to $20 \mu\text{g}/\text{day}$.

In sum, the proposed listing of "diesel particulates" is not warranted based on the current understanding of diesel particulate matter. Consequently, this fundamental issues must be addressed before the NTP advances any further in the pending listing process.

2. **Opinions About "Causal" Relationships Do Not Fairly Represent The Data And Are Unjustified**

Opinions that selected epidemiological studies provide evidence consistent with a causal relationship between occupational diesel exhaust exposure and lung cancer have been expressed by some. EMA believes that such opinions are not well-founded in data.

As Dr. Suresh Moolgavkar of the Fred Hutchinson Cancer Institute previously observed in his September 25, 1997 correspondence to OEHHA, "[n]o meta-analysis can correct for the deficiencies of individual studies, which remain a real concern with epidemiological studies of diesel exhaust." This is especially true in this case where the key epidemiological studies at issue lack any contemporaneous exposure data or characterizations of the actual emissions from the postulated sources of exposure. Indeed, as Dr. Debra Silverman of the National Cancer Institute (NCI) has stated, "[t]he repeated findings of small effects coupled with the absence of quantitative data on historical exposure, precludes a causal interpretation." (Epidemiology, Jan. 1998, Vol. 9, No. 1, p. 5.) (Emphasis added.)

In fact, there is no actual occupational diesel exhaust exposure data for the "best" studies. Indeed, if regulatory bodies were to characterize the state of the science accurately, their reports could only refer to a supposed association with "occupations/job categories deemed to have various estimated exposures to differing levels of emissions from 30-40 year-old diesel locomotive engines." Accurately describing what "exposure"

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was examined in the epidemiological studies at issue readily identifies their limited relevance and utility.

Moreover, any causal conclusions/opinions are directly contrary to the independent meta-analyses conducted to date. For example, Drs. Stöber and Abel concluded in their 1996 report that "[t]here is no causal relationship between diesel exhaust inhalation and lung cancer" and that "there is certainly not any good evidence of a dose-response relationship" (p. S-41) (emphasis added). Stöber and Abel, Lung Cancer Due To Diesel Soot Particles In Ambient Air?, Occup. Environ. Health, No. 68 (1996). In their 1995 report, Muscat and Wynder stated that "[u]sing common criteria for determining causal associations, the epidemiologic evidence is insufficient to establish diesel engine exhaust as a human lung carcinogen" (p. 812). Muscat and Wynder, Diesel Exhaust and Lung Cancer: An Unproven Association, Environ. Health Prospect., No. 103 (1995). See also L.A. Cox, Does Diesel Exhaust Cause Human Lung Cancer?, Risk Analysis, Vol. 17, No. 6, 1997.

Similarly, in the January issue of Epidemiology, Dr. Silverman of NCI commented as follows:

Bhatia et al. conclude that the data support a causal association between diesel exhaust and lung cancer in humans. Has science proven causality beyond any reasonable doubt? Probably not. The repeated findings of small effects, coupled with the absence of quantitative data on historical exposure, precludes a causal interpretation. To establish causality will require well designed epidemiological studies that do not suffer from the weaknesses of previous studies.

(Epidemiology, Jan. 1998, Vol. 9, No. 1, p. 5.)

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Also of note is a 1997 review authored by Morgan, Reger and Tucker (see Ann. Occup. Hyg., Vol. 41, No. 6, 1997, pp. 643-58). In this review, Morgan et al. find that "[a]lthough there have been a number of papers suggesting that diesel fumes may act as a carcinogen, the weight of the evidence is against this hypothesis." (Emphasis added.)

Other recent findings confirm this. For example, it has come to EMA's attention that a report was published in 1997 (and also 1995) in the Australian and New Zealand Journal of Public Health (Vol. 21, No. 1) detailing an occupational study of nearly 24,000 coal miners in New South Wales over a 20-year period (1973-1992). This cohort study was designed to describe the incidence of cancer and was constructed from the medical examination records of the Joint Coal Board. Significantly, this large cohort study found no increased risk for lung cancer among the study population. To the contrary, the reported SMR for lung cancer was 0.74 (CI = 0.50 to 1.06). See also The Medical Journal of Australia, Vol. 163, July 1995, pp. 19-21.

In the face of this current body of evidence, reliance on the 1988 IARC listing of diesel exhaust as "probably carcinogenic" as continuing support for an asserted finding of a causal association is no longer justified. The IARC listing was premised primarily on "sufficient evidence for the carcinogenicity in experimental animals of extracts of diesel engine exhaust particles." (See IPCS Report No. 171, p. 289.) As evidenced by the latest publications of Dr. Joe Mauderly and others, however, current scientific

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understanding suggests that the animal data likely are not relevant to humans, a circumstance which calls the entire basis for IARC's listing into question. Indeed, members of the original IARC panel have stated recently that diesel exhaust would not be considered as a Group 2A carcinogen if reevaluated based on current scientific understanding.

The claim for a causal role for diesel exhaust in the epidemiologic studies also is severely undermined by the fact that the relative risks reported for lung cancer for a variety of occupations are remarkably similar, even though the estimated diesel exhaust exposures from occupation to occupation covered a three-order-of-magnitude range. As stated by Dr. Moolgavkar in his September 25, 1997 comments to OEHHA,

I also noted that some of the results of the meta-analyses were rather unexpected. For example, the level of risk in different occupational categories was rather similar, which is surprising in view of the different levels of exposure to diesel exhaust in different occupations.

More specifically, the OEHHA summary meta-analysis value for all diesel exhaust epidemiologic studies has been reported at 1.33, with a range of 1.11 to 1.49 in the subanalysis by occupation. Even in the absence of actual exposure data, it seems implausible that, if diesel exhaust were causally increasing lung cancer risk by approximately 40% for low exposure (e.g. truck drivers), the lung cancer risk derived for more heavily exposed worker populations (e.g. railroad workers and miners) would fall into the same estimated narrow range of small added risk.

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For example, if diesel exhaust concentrations for truck drivers in the range of 10-20 $\mu\text{g}/\text{m}^3$ produced a relative risk of 1.49 (the meta-analysis result), we can assign the 0.49 excess risk to the 10-20 $\mu\text{g}/\text{m}^3$ exposure. Consequently, diesel exhaust concentrations for underground miners in the range of 1000-2000 $\mu\text{g}/\text{m}^3$ should have yielded excess risks 100 times larger than 0.49, or 49, meaning that the relative risk for diesel-exhaust-exposed underground miners would be expected to be 50 (1 + 49), whereas the actual reported relative risks range from 1.45 - 2.67 (0.74 for the Australian coal miners cohort). Such a complete lack of concordance strongly argues against a causal role for diesel exhaust in the reported epidemiologic associations.

Moreover, the NCI itself has commented specifically on weak relative risks, stating

In epidemiological research, relative risks of less than 2 are considered small and are usually difficult to interpret. Such increases may be due to chance, statistical bias, or effects of confounding factors that are sometimes not evident. (NCI, 1994)

In sum, what the Health Effects Institute ("HEI") stated in 1995 still holds today. The results of the epidemiological studies -- which include at least ten studies with SMR's less than 1.0 (see Risk Analysis, Vol. 17, No. 6, 1997, p. 812) -- exhibit a "weak association" between occupational exposure to diesel exhaust and lung cancer, but there is insufficient evidence to conclude whether confounding by other factors influenced the results. (HEI Report, p. 6.)

3. The Bioavailability Of The Organic Fraction Of Diesel Exhaust Particulate Matter Has Not Been Demonstrated

Relying on particulate extracts as a surrogate of diesel exhaust incorrectly attributes a genotoxic role to diesel particles without recognizing that the organic fraction must first be extracted by strong solvents and concentrated before any mutagenic action can be demonstrated. Moreover, laboratory studies have shown that particles dissociate much more slowly in vivo than when extracted by organic solvents in vitro, and that serum and tissue cytosols significantly reduced the cytotoxicity of diesel particulate extracts. As a result, mutagenic effects obtained through the testing of solvent extracts may well have falsely postulated effects that do not occur in living organisms.

Moreover, the direct application of unusually high concentration gradients does not replicate the actual contact of diesel particles with cells in the human body. Because most evidence of genotoxic action of whole diesel particles or exhaust have been obtained either by using concentrated solvent extracts of diesel particles or extremely high concentration gradients (mg mass per ml of media or tissue culture), there is an obvious lack of relevance of these studies for actual conditions that are encountered in vivo after ambient exposures (i.e. $1.5 \mu\text{g}/\text{m}^3$).

Indeed, when the concentrations utilized in the studies at issue are recalculated in terms of lung surface distribution or distribution in body fluid, it becomes clear that the studies involve completely unrealistic accumulations of particulate masses

that simply are not present in actual environmental concentrations. More importantly, such extreme situations could never occur because before the supposed genotoxic effect of such exaggerated exposures could be manifested, the whole organism would suffer from the general toxicity of such extreme exposures.

As a related point, it is improper in assessing diesel particulates to equate potential genotoxic mechanisms of carcinogenicity with the absence of a threshold in the dose-response. Such a position fails to acknowledge what is currently known about DNA repair mechanisms. Because the dose to the respiratory tract of diesel particulate at ambient concentrations is so small, it is highly unlikely that DNA repair mechanisms would be overwhelmed. Thus, the possibility of a threshold must be considered among the possible mechanisms of human responses. Indeed, the extrapolation of any data to ambient exposures encountered by the population must include the probability of a threshold, regardless of the proposed mechanism of action.

In sum, and again as HEI has correctly noted, it is simply not clear what fraction of the genotoxic material associated with diesel exhaust is bioavailable, or whether the mutagenic potency demonstrated in vitro extends to the more complex in vivo environment. (HEI Report, p. 29.)

4. The NTP Review Must Address The Critically Important Issue of Ambient Dose

NTP's emphasis should be on whether a toxic dose of diesel exhaust can be found in the environment at ambient concentrations.

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The dose of deposited particulate in the lung from an exposure concentration of $1.5\mu\text{g}/\text{m}^3$ is extremely tiny. Indeed, the daily deposited dose is less than 1 particle per 100 alveoli or less than 1 particle per 600 alveolar macrophages. This level of particle deposition will be readily ingested by macrophages, with the particles isolated within phagolysosomes.

Consideration of the systematic dose from this low level of airborne particulate suggests that the daily dose is below "no effect" levels. Indeed, the daily dose of pure arsenic judged to be without adverse health effects is 14-fold larger than the dose of diesel exhaust at issue, while the dose of cyanide judged to be without adverse health effects is 1000 times larger. NTP needs to provide comparisons of this kind so that policymakers and the public can put the potential health effects associated with diesel particulates into better perspective. Thus far, regulatory agencies have not done this, which provides an important opportunity for NTP.

Moreover, a comparison of the "mutagenic dose" of the diesel exhaust organics, even if completely bioavailable (which they are not), shows that the quantitative dose is again exceedingly small. A comparative potency analysis shows that, assuming the mutagenic activity of diesel engine exhaust is 100% bioavailable, current diesel exhaust levels result in an estimated risk equivalent to smoking one cigarette every 6 to 16 years. This would be equivalent to a person smoking three to eight cigarettes over a 70 year lifetime, starting at age 20. It is essential to provide such

perspective in the NTP review process.

**5. The NTP Review Must Account For
The Use Of New Engine Technology
And Reformulated Fuels**

NTP's review also must consider the advent of new engine technology and low-sulfur, low-aromatic diesel fuels. This is more than a little significant. In fact, the emissions from today's engines running on today's fuels are dramatically different from the estimated emissions to which railroad workers may have been exposed back in the 1960's and 1970's.

On or about April 3, 1998, the California EPA released a draft report prepared under contract by the College of Engineering - Center for Environmental Research and Technology (CE-CERT) of UC Riverside, entitled "Evaluation of Factors that Affect Diesel Exhaust Toxicity" (hereinafter, the "CE-CERT Report"). This CE-CERT Report details certain of the air quality (and public health) benefits resulting from the use of post-1993 diesel fuels.

The data in the CE-CERT Report are very significant and indicate that the potential toxic compounds contained in diesel exhaust are becoming much smaller contributors to overall emissions through the use of new fuels, even before factoring in the benefits derived from the use of current engine technologies. More specifically, and as evidenced in part by Figure 27 of the CE-CERT Report (p. 139), emissions of total mutagenic compounds have been reduced by 50%-60% through the now-mandated use of low aromatic fuels. Bioassays conducted by CE-CERT have confirmed that emissions from engines running on reformulated fuels exhibited

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lower mutagenic activity. (CE-CERT Report, p. 176.) In addition, emission rates of particulate matter have been reduced by up to 25% compared to pre-1993 fuels (CE-CERT Report, p. 170), while emission rates for volatile organic compounds have been reduced by similar amounts.

Other specific findings from the CE-CERT data bear special note. For example, nitroaromatic compounds have been identified in diesel particle extracts as the chemical agent responsible for the mutagenic effects in Salmonella bioassays conducted in the late 1970's and early 1980's. Using sensitive Thermosorb cartridges, data from the CE-CERT project show, however, that N-nitrosomethylamine and N-nitrosodipropylamine are detected in today's diesel exhaust only at levels that are close to their detection limits. Further, reformulated fuel emissions yield other levels that are non-detectable (no other nitrosamines including nitrosomorpholine were detected).

These findings clearly call into question the relevance of prior epidemiological studies of estimated occupational exposures to locomotive engine emissions that may have occurred 30-40 years ago, especially since those studies included no contemporaneous exposure data whatsoever. These findings also severely undermine prior opinions regarding genotoxicity, bioavailability and causality.

6. **Quantitative Risk Assessments For Diesel Particulates Are Not Justified**

EMA has repeatedly stated its strong opposition to any quantitative risk assessment constructed on the basis of existing epidemiological studies, including the Garshick et al. studies of railroad workers. Even Dr. Garshick himself has stated in correspondence to OEHHA dated August 11, 1997, as follows:

I do not believe that your current document fully expresses the uncertainty of the estimates of risk that you have presented [I]t is not possible to use a positive slope to definitely describe the relationship between cumulative exposure and lung cancer mortality. I believe that the use of a slope as derived in the OEHHA assessment has not been justified.

EMA is not alone in the view that quantitative risk assessments premised on existing studies lack adequate scientific basis. HEI has stated unequivocally that "the lack of definitive exposure data for the occupationally exposed study populations precludes using the available epidemiological data to develop quantitative estimates of cancer risk." (HEI Report, p. 8.) Similarly, WHO's 1996 report declares in unequivocal terms that "[a] quantitative risk assessment cannot be conducted on the basis of epidemiological data in which job title was used as a surrogate of exposure Consequently, there are no human data suitable for estimating unit risk." (IPCS Report No. 171, p. 254.)

Conclusion

It is imperative that NTP's review of whether "diesel particulates" should be listed in the 9th Report be completed through an objective, even-handed assessment of what the available science does and does not tell us about the potential health effects of diesel particulates. In that regard, the words of Dr. Silverman of NCI bear repeating:

Has science proven causality beyond any reasonable doubt? Probably not. The repeated findings of small effects, coupled with the absence of quantitative data on historical exposure, precludes a causal interpretation. To establish causality will require well designed epidemiological studies that do not suffer from the weaknesses of previous studies.

. . . . The scientific community has a responsibility to continue to pursue the question of whether diesel exhaust is a human carcinogen, a task beyond the limits of a meta-analysis of existing studies.

EMA is committed to pursuing new, well-designed epidemiological studies to further our understanding of these important issues and has committed its financial resources to such efforts. Pending the results of those efforts, however, the adverse conclusions postulated by certain agencies such as OEHHA remain unjustified by the best available scientific data. EMA therefore encourages NTP to assist in the procurement of new data and to curtail the misapplication of old studies that necessarily will remain scientifically insufficient for either causal conclusions or attempted quantifications of what are otherwise only weak associations.

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With the foregoing in mind, EMA respectfully submits the following documents (copies enclosed) containing relevant information concerning NTP's possible listing for "diesel particulates":

i) Issue: Lack of Evidence for Causal Inference by Epidemiology Studies (2/6/98);

ii) Correspondence dated January 19, 1998 from Dr. Joe L. Mauderly to Glenn F. Keller (with attachments);

iii) Reprint from Environmental Health Perspectives, Volume 103, No. 7-8 (July-August, 1995);

iv) Relation Between Exposure to Diesel Emissions and Dose to the Lung (HEI Report 1995);

v) Does Diesel Exhaust Cause Human Lung Cancer? Risk Analysis, Vol. 17, No. 6, (1997);

vi) Memorandum dated February 4, 1998 from Nicholas Barsic to Glenn Keller re: smoking as a confounder;

vii) Integrating Diverse Data Sets to Assess the Risks of Airborne Pollutants, ILSI Monograph (1989);

viii) Epidemiologic Studies of Populations Exposed to Motor Vehicle Exhaust and Polycyclic Aromatic Hydrocarbons, M.B. Schenker;

ix) Assessment of Inhalation Hazards, ILSI Monograph;

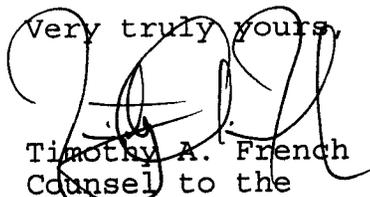
x) Comments of the Engine Manufacturers Association Regarding the ARB/OEHHA Draft Report "Proposed Identification of Diesel Exhaust as a Toxic Air Contaminant, May 1997" (August 1997);

xi) Comments of the Engine Manufacturers Association Regarding the ARB OEHHA Draft Report "Proposed Identification of Diesel Exhaust as a Toxic Air Contaminant, February, 1998" (March, 1998).

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Thank you for your careful consideration of EMA's comments and the information set forth in the enclosed documents. If you have any questions concerning these matters, please do not hesitate to contact us.

Very truly yours,

A handwritten signature in black ink, appearing to read 'T. French', is written over the typed name and title.

Timothy A. French
Counsel to the
Engine Manufacturers Association

/Enclosures

cc: Glenn F. Keller
Nicholas J. Barsic
Jed R. Mandel

Issue: Lack of Evidence for Causal Inference by Epidemiology Studies

Background

Earlier in our discussions the Engine Manufacturers Association (EMA) commented on the inaccurate conclusion reached by OEHHA that "a reasonable and likely explanation for the increased rates of lung cancer observed in the epidemiological studies is a *casual association* between diesel exhaust exposure and lung cancer" (See, Executive Summary page ES-12, third paragraph). A closer examination of the epidemiological studies performed on diesel occupational exposure reveals inconsistencies between the concentration of diesel exposure in the occupational groups and their observed increase in relative risk for cancer.

Shortly following our 7 Jan 98 conference call EMA submitted to OEHHA an article authored by Dr. Peter Valburg entitled: **Comparison of Diesel-Exhaust Epidemiology Relative Risks with Diesel-Exhaust Concentration Measurements**, January 1998. This article set forth the findings of Dr. Valburg's investigation of the small range of relative lung cancer risks attributed to diesel exhaust (DE) by all the various epidemiology studies of occupational exposures over an extremely broad range of particulate concentrations. The occupational groups studied were exposed to concentrations of DE spanning three orders of magnitude from units to thousands of $\mu\text{g}/\text{m}^3$ (e.g., with truck drivers at the lowest $\sim 10\text{-}20 \mu\text{g}/\text{m}^3$; railroad workers, bus garage workers at $\sim 50\text{-}500 \mu\text{g}/\text{m}^3$; and underground miners at $\sim 1,000\text{-}2,000 \mu\text{g}/\text{m}^3$). Yet in spite of this three-order-of-magnitude difference in the potential for DE particulate exposure, the epidemiologic relative risks observed cluster in an extremely narrow range of 1.11 to 1.49.

This discrepancy across epidemiology studies can be determined by a sample calculation that assumes (as OEHHA does) that the lung cancer risk is linear with DE concentration (exposure). For example, if DE concentrations for truck drivers in the range of $10\text{-}20 \mu\text{g}/\text{m}^3$ produced a relative risk 1.49 (the meta-analysis result), we can assign the 0.49 excess risk to the $10\text{-}20 \mu\text{g}/\text{m}^3$ exposure. It would then follow from this that for underground miners in the range of $1,000 - 2,000 \mu\text{g}/\text{m}^3$ should have yielded excess risks one hundred times larger, or 49, meaning that the relative risk for underground miners would be expected to be 50 (1+49), whereas the reported relative risk range from 1.45 - 2.67. Valburg's analysis raises the distinct possibility that in all the occupational exposure studies a consistent confounding element or bias may be acting in negating the assumed linear relative risk relationship to cumulative diesel exposure. Therefore, it is inaccurate to conclude that the results of the 30 human studies are consistent results and unlikely to be due to chance, confounding, or bias.

Such a lack of agreement in the resultant range of relative risk across the epidemiology studies does not support a conclusion that diesel exhaust exposure was the behind the uniform increase of cancer incidence observed in the cohorts. The resultant discrepancy observed would argue that there is another exposure factor operating in the background that is a constant across all the occupational groups that may be responsible for the uniform increment of relative risk found in the various exposed occupational groups.

When comparing lung cancer risk and reported diesel exhaust concentrations, it is essential to recognize three characteristics of the diesel-exhaust epidemiology.

None of the epidemiology studies include measurements of the actual diesel exhaust concentrations encountered for the study populations. For the majority of studies, the potential for DE exposure was indirectly assessed from union records, interviews, questionnaires, and death certificates. Furthermore, there were no actual exposure measurements of individual study subjects.

Most of the epidemiology studies have inadequate (or nonexistent) control for confounders such as smoking, ETS exposure, or other ambient-air particles. Therefore, the lung cancer risk reported may have not have a direct causal relationship to presumed personal diesel exhaust exposure.

Most of the measurements relating to diesel exhaust exposure are for "particulate concentrations." Investigators have attempted in various ways to correct for other sources of ambient particulate such as dust, ETS or gasoline engine exhaust, but it should be remembered the entire reported concentration may not be diesel exhaust particulate. Thus the observed health effect may be due to a substance other than diesel exhaust.

Although comparisons have been made between reported lung cancer risks and occupational diesel exhaust exposure concentrations, it must be acknowledged that any quantitative relative risk calculations derived from these studies are uncertain due to the fact that there are no human epidemiology studies with actual measures of diesel exhaust exposure for the study population at the time they were exposed. Moreover, continuous improvements that have occurred in factors such as diesel fuel formulation, engine design, workplace ventilation, and worker smoking habits hinder retrospective application of the measure particulate exposure values collected at a much later date in time.

It is remarkable to note that the range of relative lung cancer risks attributed to diesel exposure by the various epidemiology studies cover such a small range. That is, the reported results cluster in the range from no added risk (1.0), up to about a doubling of risk (2.0), with a few values above this level. In fact, the summary meta analysis value for all diesel exhaust epidemiology studies is 1.33, with a range of 1.11 to 1.49 in the subanalysis by occupation (Bhatia *et al.*, 1998). Even in the absence of diesel exposure data, it seems implausible that, if diesel exhaust were the cause for increasing lung cancer risk by 50% for low exposure (say, truck drivers), the lung cancer risk for diesel exhaust produced in more heavily exposed worker populations (railroad workers or miners) would be found to fall in this same range of added risk. The above comparison does raise the possibility that a consistent confounding element or bias may be unaccounted for in the background of all the occupational exposure studies that could have produced the narrow range of relative risk values observed in all the human studies despite the fact they had a substantial three-orders-of-magnitude range of diesel exhaust exposure concentration across the occupational cohorts. However, it would be difficult to ascertain the cause for this discrepancy given that no actual exposure measurements were taken during these studies to enable an identification of any potential confounders that may be responsible for the narrow range of observed relative risk.



Respiratory Research Institute

12764

January 19, 1998

Glenn F. Keller
Executive Director
Engine Manufacturers Association
401 North Michigan Ave.
Chicago, Illinois 60611-4267

Dear Glenn:

I am providing the enclosed paper as the most recent written summary of the current information concerning the scope and relevance of animal data for judging the health risks from inhaled diesel exhaust. This material is excerpted from a manuscript for a chapter to be published in the second edition of the text, ENVIRONMENTAL TOXICANTS: Human Exposures and Their Health Effects, edited by Dr. Morton Lippmann. This is an update of the chapter in the 1992 first edition, which has been quoted by EPA, CARB, and other organizations. Dr. Lippmann has reviewed this material and has granted approval for its circulation as a prepublication excerpt from the chapter manuscript, which has just now been submitted. I do not know the publication date of the chapter, but it will probably be late this year.

My purpose in sending this material is to provide a written, referenced summary of my understanding of the current data from animal studies pertaining to the cancer risk from inhaled diesel exhaust. Although I have spoken on this topic many times, the enclosed material constitutes the only written summary of which I am aware that portrays completely the most recent findings and our current understanding and interpretation of the relevance of the rat lung tumor response to estimation of human lung cancer risk from diesel exhaust.

There is a compelling scientific case against using the rat tumor data for estimating human risk, and each addition piece of information that accumulates appears to strengthen that case. The irrelevance of the rat data does not, by itself, make the case that there is no risk at all. Regardless, I take the position that the rat data can not be used to declare, or quantitatively estimate, such risk, and by extension, should not be used to place bounds around such risk.

You are welcome to distribute this material to others as you think appropriate. I have provided copies to EPA, CARB (Denton, Alexeff, SRP), Stephanie Williams, Bill Bunn, Michael Spallek, and others. I welcome the opportunity to respond to any questions you or others might have about this material or the issues to which it pertains.

Sincerely;

Joe L. Mauderly, DVM

JLM/jm
Encl: manuscript

Curing Respiratory Disease

SECTION ON ANIMAL STUDIES FROM REVISED CHAPTER ON DIESEL EXHAUST:

Mauderly, J. L.: Diesel Exhaust. In *Environmental Toxicants: Human Exposures and Their Health Effects*, Chapter 5, (M. Lippmann, ed.), pp. 119-162, Van Nostrand Reinhold Publishers, New York, NY, 1992.

NOTE: The following material is excerpted from a revision of the above chapter, which was recently submitted to the publisher and will appear in the second edition of the book. Headings for other sections are included to place the information in context, but text other than that related specifically to the animal data is excluded. Only the tables, figures, and references related to the text given here are included.

INTRODUCTION

EXPOSURES TO DIESEL EXHAUST

Composition of Diesel Exhaust and Potential Toxicity of Exhaust Components

Particulate Phase

Gas and Vapor Phases

Emission Standards and Current Exposure Levels

HEALTH EFFECTS

Lung Cancer

Epidemiology

Cohort Studies

Case-Control Studies

Combined Analysis of Multiple Studies

Summary of Epidemiological Evidence

Animal Studies

In the absence of definitive data from humans, hazard characterization and risk assessment typically use data from animals exposed experimentally to the agent in question. Regarding the carcinogenicity of diesel exhaust however, results from animals have not proved to be very helpful. The history of laboratory carcinogenicity studies of diesel exhaust is interesting because, despite the large amount of experimental data

accumulated over the past 20 years and despite the dose-related lung tumor response of rats, our present knowledge indicates that this information should not be used for estimating human lung cancer risk, and is of questionable value in determining carcinogenic hazard. Regardless, the animal studies of the cancer risks from inhaled diesel exhaust are summarized in this chapter for historical perspective and as a foundation for understanding their lack of utility for estimating human cancer risk.

Unlike epidemiological studies, studies of the health effects of inhaled diesel exhaust in laboratory animals can be conducted under carefully-controlled, well-documented experimental conditions that allow the effects to be quantitated precisely. Although the groups of animals are smaller (typically 50 to 200) than in most epidemiological studies, animal experiments gain statistical strength from their designs and the precision of the data. Nevertheless, studies of animals are bound by the same statistical rules as studies of humans, and even groups of 200 rodents do not have the statistical power to determine the significance of a 20% to 50% increase in lung tumor incidence against a variable background incidence of up to 3%. Statistics aside, the greatest difficulty with animal studies is the uncertainty of extrapolation across species. Confidence in extrapolating the results to humans is gained if similar responses are observed in more than one animal species. An increased tumor incidence in animals is generally accepted as signaling a potential carcinogenic hazard for humans. However, extrapolating the animal response to quantitative estimates of cancer risk requires confidence that: 1) the mechanisms by which cancer occurred in animals are likely to also operate in humans; and 2) the exposure-dose-response relationship observed in animals at high levels of exposure can be extended downward to the much lower levels of human exposure. The following information summarizes results from experimental exposures of rats, mice, and Syrian hamsters, the only species with which near-lifetime inhalation carcinogenesis bioassays of diesel exhaust have been conducted.

Studies of Rats

The published studies of pulmonary carcinogenicity in rats exposed chronically to diesel exhaust are summarized in Table 8-4. For studies described in multiple publications, the reference given is the most complete description. Early descriptions of several of the studies, in some cases presenting ancillary results not contained in the citations below, were published by Ishinishi et al. (1986). The experimental details are only briefly outlined, both because they were not reported in detail by all authors, and because variables other than soot concentration and exposure time have not proven to strongly influence the outcome. Eight studies involved exposures of 24 months or longer and used groups of 50 or more rats, the minimum number generally considered adequate for testing carcinogenicity.

Heinrich et al. (1986) exposed 96 rats/group, 19 hr/day, 5 days/week for 32 months to exhaust at 4.2 mg soot/m³, resulting in a 15.8% incidence of lung tumors in contrast to none in controls. A key finding was that a parallel group (not listed in Table 8-4) exposed to the same concentration of exhaust with the soot removed by filtration had no increase in lung tumor incidence.

Mauderly et al. (1987) exposed 220 rats/group, 7 hr/day, 5 days/week for 30 months at 0.35, 3.5, and 7.1 mg soot/m³, resulting in lung tumor incidences of 1.3%, 3.6%, and 12.8%, respectively, in contrast to 0.9% among controls. The increases in tumor incidence were significant for the two higher concentrations. In another study conducted later using identical exposures, Mauderly et al. (1986, 1990b) exposed 80 rats/group, 7 hr/day, 5 days/week for 30 months at 3.5 mg soot/m³ and observed a 6.5% lung tumor incidence in contrast to none among controls.

Ishihara (1988) conducted concurrent studies of rats exposed 16 hr/day, 6 days/week for 30 months to exhaust from light-duty and heavy-duty engines. The heavy-duty exhaust was administered at 0.5, 1.0, 1.8, and 3.7 mg soot/m³, resulting in lung tumor incidences of 3.3% and 6.5% at the two highest levels, respectively. The highest tumor incidence was significantly elevated above the 0.8% incidence among controls.

Brightwell et al. (1989) exposed 144 rats/group, 16 hr/day, 5 days/week for 24 months to exhaust at 0.7, 2.2, and 6.6 mg soot/m³, and observed the rats for an additional 6 months. The lung tumor incidences at the two highest levels, 9.7% and 38.5%, were significantly increased above the 1.2% incidence among controls. In agreement with the Heinrich et al. (1986) study above, parallel groups of rats exposed to the two higher concentrations of exhaust with the particles removed by filtration (not listed in Table 8-4) had no increase in lung tumor incidence.

Lewis et al. (1989) exposed 180 rats/group, 7 hr/day, 5 days/week for 24 months to water-scrubbed exhaust from a mine engine at 1.95 mg soot/m³ and observed a slight but insignificant increase in lung tumor incidence.

Heinrich et al. (1995) exposed 100–220 rats/group 18 hr/day, 5 days/week for 24 months to exhaust at 0.8, 2.5, and 7.0 mg soot/m³ and observed the surviving rats for an additional 6 months. The lung tumor incidence was increased significantly at the highest exposure level.

Nikula et al. (1995) exposed 210–214 rats/group 16 hr/day, 5 days/week for 24 months to exhaust at 2.4 and 6.3 mg soot/m³, and observed a dose-related increase in lung tumor incidence that was statistically significant at both exposure levels.

Only two of the above eight studies did not yield statistically significant increases in lung tumor incidence in rats, the light-duty engine study by Ishihara and the mine engine study by Lewis et al. Interestingly, these two studies also yielded the highest incidences (3.3%) of lung tumors in control rats; control incidences in the other studies ranged from 0% to 1.2%. It is doubtful that a lower control incidence would have influenced the statistical outcome of the Ishihara et al. study, but a lower control incidence might have yielded significant increases in the Lewis et al. study. The highest exposure level in both of these studies was approximately 2 mg soot/m³ which proved to be just below the approximate threshold for a tumor response when data from all the studies were considered in aggregate.

Five of the studies listed in Table 8-4 used treatment groups of only 15–34 rats or exposure or observation periods that were too short for expression of carcinogenesis. Of those studies however, only that of Takemoto et al. (1986) did not produce a greater incidence of lung tumors among exposed rats than among controls.

These results demonstrate clearly that the soot fraction of diesel exhaust is a pulmonary carcinogen in rats exposed in sufficient numbers at sufficiently high concentrations for sufficiently long times. The aggregate exposure-response relationship from the eight most robust studies is illustrated in Fig. 8-1, in which the net (exposed minus control) tumor incidences are compared on the basis of the exposure rate, or weekly concentration-time product ($\text{mg}\cdot\text{hr}\cdot\text{m}^{-3}$). Two key points can be drawn from the graph. First, the data generally fall into three exposure-response groupings and strongly suggest a threshold. Exposure rates below approximately $100 \text{ mg}\cdot\text{hr}\cdot\text{m}^{-3}$ produced no suggestion of a tumor response; i.e., no suggestion of a response slope. Exposure rates between approximately 100 and $250 \text{ mg}\cdot\text{hr}\cdot\text{m}^{-3}$ produced an intermediate zone of variable response, including some significant responses, some insignificantly elevated responses, and one group with no increase at all. All exposure rates above approximately $250 \text{ mg}\cdot\text{hr}\cdot\text{m}^{-3}$ produced significant increases in tumor incidence. Second, diesel exhaust proved to be only a weak carcinogen in rats, even at the higher exposure rates. One group had a net tumor incidence of 37%, but none of the others exceeded 15%.

Studies of Mice

There are six reports of carcinogenicity results from mice exposed chronically by inhalation to diesel exhaust (Table 8-5). Two studies used strains (Sencar and Strain A) which have high background incidences of lung tumors and were developed for their sensitivity to chemical carcinogens. Using exposures of only 7.5 to 15 months, these studies are a different type of carcinogenicity bioassay than the others conducted in mice, rats, and hamsters. The other four studies used longer-term exposures of strains commonly used in chronic inhalation cancer bioassays, and are more useful for interspecies comparisons.

Heinrich et al. (1986) exposed female NMRI mice 19 hr/day, 5 days/week for 28 months to exhaust at $4.2 \text{ mg soot}/\text{m}^3$ and observed a significant increase in lung tumors. Interestingly, parallel exposures of mice to the same dilution of exhaust with the soot removed by filtration (not shown) also increased the lung tumor incidence, in contrast to the finding of no increased carcinogenicity in rats exposed to filtered exhaust in the parallel study.

Takemoto et al. (1986) exposed male and female C57BL/6N and ICR/Jcl mice 4 hr/day, 4 days/week for 28 months to exhaust at $2\text{--}4 \text{ mg soot}/\text{m}^3$ (mean concentration not reported) and observed modest increases in lung tumor incidence; the significance of the increases was not reported.

Heinrich et al. (1995) exposed female NMRI and C57BL/6N mice 18 hr/day, 5 days/week for 23 (NMRI) or 24 months to exhaust at 4.5 mg soot/m³. The lung tumor incidence of exposed NMRI mice was lower than that of controls, and that of exposed C57BL/6N mice was slightly, but not significantly, higher than that of controls. They also exposed female NMRI mice 18 hr/day, 5 days/week to exhaust at 7.0 mg soot/m³ for 13.5 months followed by a 9.5 month observation period. The lung tumor incidences in exposed and control mice were nearly identical.

Mauderly et al. (1996) exposed male and female CD-1 mice 7 hr/day, 5 days/week for 24 months to exhaust at 0.35, 3.5, and 7.1 mg soot/m³, concurrent with the rat study reported earlier (Mauderly et al. 1987). The lung tumor incidence at the low level was slightly (insignificantly) higher than that of controls, and the incidences at the higher two levels were lower than that of the controls.

The studies of Pepelko and Peirano (1983) yielded mixed results using Strain A and Sencar mice. Exposures of Strong-A mice 8 hr/day, 7 days/week for 7.5 months at a soot concentration of 6.0 mg/m³ yielded a significantly positive response in a group of females, but no increase in a parallel group of males. In contrast, two other combined male-female groups exposed at 12 mg soot/m³ yielded significantly reduced lung tumor incidences. An exposure of male Jackson-A mice on the same weekly schedule for 10.5 months at a 12 mg soot/m³ yielded a significantly reduced lung tumor incidence. Exposures of Sencar mice from birth on the same weekly schedule for 15 months at 6 mg soot/m³ for the first 12 weeks and then 12 mg soot/m³ for thereafter yielded a significantly positive response in females, but not in males.

The above results indicate that mice have, at most, an equivocal lung tumor response to diesel exhaust. The positive results obtained in female NMRI mice by Heinrich et al. (1986) were not reproduced in their later study (Heinrich et al. 1995). All other results in common bioassay strains were negative. The results from genetically-susceptible strains were mixed. Overall, it is clear that the consistently positive response of rats produced by high-level exposures were not reproduced in mice. Although the life span of mice is typically shorter than that of rats, life-span shortening in exposed mice did not compromise the comparison to controls (Heinrich et al. 1995; Mauderly et al. 1996).

Studies of Syrian Hamsters

There are five reported studies of Syrian golden hamsters exposed chronically to diesel exhaust (Table 8-6). Groups of 30–410 male and female hamsters have been exposed for times ranging from 15 months to lifetime to exhaust at concentrations ranging from 0.25 to 7.3 mg soot/m³. Not a single lung tumor has been observed in diesel exhaust-exposed hamsters; therefore, diesel exhaust is clearly not a pulmonary carcinogen in Syrian hamsters exposed under conditions carcinogenic in rats.

Usefulness of Experimental Data for Assessing Lung Cancer Hazard and Risk

It is not broadly questioned that the organic fraction of diesel soot can be considered to present a carcinogenic hazard. The identification of hazard is fulfilled by the confirmed presence of mutagenic and carcinogenic chemical species, the mutagenicity of soot extract in bacteria and mammalian cells, and by its carcinogenicity in the mouse skin painting assay (Kotin et al. 1955). However, the identification of inhaled diesel soot as a lung cancer hazard is more controversial. As described above, lung tumor induction by inhaled soot has been consistently demonstrated only in rats, and is not supported by results from other species. As described below, there is convincing evidence that the lung tumor response of rats to diesel soot should not be used for quantitative estimates of human lung cancer risk. For the same reasons, it is doubtful that the rat lung tumor response is a useful indicator of lung cancer hazard for humans.

In the face of poor ability to confidently estimate quantitative lung cancer risks from environmental exposures to diesel exhaust from epidemiological data, it appeared logical to turn to the exposure-response relationships from the rat lung tumor data. A number of estimates of human lung cancer risk per unit of exposure have been derived by modeling the rat data (reviewed in Mauderly 1992; EPA 1994; HEI 1995; Cal EPA 1997), and at least one such estimate has been used by a regulatory agency to predict diesel exhaust-related cancer deaths (EPA 1993). However, our current knowledge indicates that the rat lung tumor data should not be used for developing estimates of unit lung cancer risk for humans exposed to environmental levels of diesel exhaust (CASAC 1995; McClellan 1996; Mauderly 1997a), and probably should not be used for estimating risks from even much higher occupational exposures. Although this conclusion is supported by a substantial base of information gained progressively over the last 15 years, it goes contrary to default risk assessment practices and is not well understood by all stakeholders in the issue. For these reasons, the critical pieces of evidence for this conclusion are reviewed here.

1. *The cellular responses of the rat lung to diesel soot are strikingly different from the responses of other rodents.* During chronic exposure, soot accumulates in foci in the rat lung and causes a progressive inflammatory and fibrotic lesion accompanied by sustained increased proliferation of alveolar Type II cells and bronchiolar Clara cells, the cell types thought to give rise to the lung tumors. Another characteristic response of the rat lung epithelium to heavy, chronic particle exposure is the development of squamous keratin cysts (Nikula et al. 1995; Mauderly 1996), which have sometimes been described as “benign keratinizing cystic squamous cell tumors” (Heinrich et al. 1995). Cuboidal and squamous epithelial metaplasias are typical of rat lungs after months of heavy exposure. Under identical conditions, soot tends to remain more widely dispersed in mouse lungs and has much less tendency to cause focal lesions (Mauderly 1996). Although the size-adjusted lung burdens of soot are equivalent in rats and mice exposed identically, the inflammatory response is less in mice (Henderson et al. 1988). The magnitude and persistence of epithelial

proliferation characteristic of rat lungs are not characteristic of mice (Mauderly 1997b). Although epithelial hyperplasia is sometimes observed in mice after long-term exposure, epithelial metaplasia is not common (Mauderly et al. 1996). Squamous keratin cysts are not a typical response of mouse lungs to particle exposure; only one lesion having similar characteristics has been reported in a diesel-exposed mouse (Mauderly et al. 1996). The same differences are found between rats and hamsters. This evidence indicates that the bronchiolar and alveolar epithelium of the rat is somehow predisposed to respond quite differently than the epithelia of mice and hamsters to chronic, heavy exposures to diesel soot and other particles. It seems likely that epithelial neoplasia (the formation of tumors) in exposed rat lungs is an extension of the hyperplastic and metaplastic epithelial changes typical of that species.

2. *The epithelial response of rat lungs to diesel soot is not typical of nonhuman primates, and is not thought to be typical of humans.* The key issue is not comparisons among animals, but whether or not the lung epithelial proliferative changes in rats that appear to advance to neoplasia are characteristic of humans. Opinions of pathologists expert in human pulmonary responses to heavy dust exposure indicate that epithelial proliferative responses paralleling those of rats are not characteristic of human lungs (personal communications, Dr. F. H. Y. Green, University of Calgary, Alberta, Canada, Dr. N. V. Vallyathan, NIOSH, Morgantown, WV, and Dr. M. Schultz, Institut fur Pathologie, Uchtspringe, Germany). Although direct comparisons between rats and humans known to be exposed identically are not possible, it is possible to directly compare responses of rats and nonhuman primates. Nikula et al. (1997) compared the pulmonary responses of rats and cynomolgus monkeys to identical chronic diesel exhaust exposures and observed clear differences between the species. They reported that, although similar amounts of soot were retained in the lungs of the two species, the predominant site of retention was alveolar in rats and interstitial in monkeys. More importantly, the epithelial proliferative responses that occurred in rats were absent in the monkeys. Although the 2 year exposure was not sufficiently long to confirm a lack of tumor response in the monkeys, there were no proliferative changes to suggest a progression that would lead to tumorigenesis. This information, along with knowledge of the typical responses of human lungs to particle loading, supports the conclusion that the proliferative response of the rat lung to diesel soot accumulation would not occur in humans.
3. *Lung cancer risk from diesel soot can not be extrapolated from rats to other rodents.* The large base of information reviewed in the preceding section illustrates clearly that it is impossible to extrapolate lung cancer risk from rats to other rodents, even under extreme exposure conditions. This interspecies difference is not unique to diesel soot, but also occurs

with chronic, heavy exposures to a number of other solid, respirable particles (reviewed in Mauderly 1997b). Twelve types of inhaled particles and fibers producing positive lung tumor responses in rats have been shown to be negative in mice. Few nonradioactive particles were positive in both species, and none were positive in mice and negative in rats. The positive carcinogenicity of the materials in rats is now attributed to a characteristic response of that species to exposures at rates that overwhelm the rate of clearance of particles from the lung, and "lung overload" has become a general term for the phenomenon. A recent symposium on the topic was summarized by Mauderly and McCunney (1996).

4. *The threshold in the rat tumor response precludes extrapolation to low exposure levels.* Even if the rat lung tumor response did mirror a likely human response, the threshold in the rat response would preclude linear projection of the exposure-response relationship down to environmental exposure levels. As described above, the data points in Figure 8-1 show a threshold for the rat lung tumor response at a weekly soot exposure rate of approximately $100 \text{ mg}\cdot\text{hr}\cdot\text{m}^{-3}$. The data are robust; confidence in the threshold is generated by the negative responses of nine exposed groups considered adequate for cancer bioassays. Further confidence in the threshold is generated by the absence of any slope among the data points within this range. Additional confidence is contributed by the negative results from detailed measurements of inflammatory, proliferative, fibrotic, and lung clearance effects at an exposure rate of $12.3 \text{ mg}\cdot\text{hr}\cdot\text{m}^{-3}$, despite the accumulation of small amounts of soot in the lungs (Mauderly et al. 1987; Henderson et al. 1988). These findings support the current view that not only tumors, but also significant nonneoplastic effects, occur in rats only if the exposure rate exceeds a functional threshold that allows substantial amounts of soot to accumulate progressively. The apparent exposure threshold for cancer of approximately $100 \text{ mg}\cdot\text{hr}\cdot\text{m}^{-3}$, if averaged over 24 hr/day, 7 days/week, would represent a continuous exposure of approximately $600 \mu\text{g}/\text{m}^3$, which is more than two orders of magnitude above estimated human environmental exposures. Even the nonneoplastic no-effects level of $12.3 \text{ mg}\cdot\text{hr}\cdot\text{m}^{-3}$ would represent an average exposure of $73 \mu\text{g}/\text{m}^3$, which is over an order of magnitude above environmental exposures.

The mathematical models which have been applied to the rat lung tumor data to estimate cancer risks from low-level exposures have generally been linearized models that assume no threshold. The assumption of a linear, no-threshold response is a common default practice in the absence of actual information on the nature of the exposure-response relationship. Because of the small numbers of exposure groups and small group sizes used in any single study, it is not surprising that even multistage linearized models applied to individual study data sets

have not demonstrated a statistically significant threshold in the response. A threshold is clearly present, however, when the aggregate data are examined (Figure 8-1). Given the availability of a substantial data base from numerous treatment groups in adequately-designed studies from several laboratories, the actual data provide a much better view of the exposure-response relationship than linearized models or default assumptions.

5. *The lung tumors in rats are not caused by the organic fraction of soot.* The concern for human lung cancer from inhaled diesel soot is founded on the soot-associated organic mutagens, and these compounds are also key to the determination that diesel soot presents a carcinogenic hazard. Therefore, the role of these compounds in the rat lung tumor response is key to the utility of that response for human risk assessment. Because of the large body of evidence that rat lungs respond similarly to a wide range of particles, many having no organic mutagens (Mauderly 1997b), independent studies were conducted in two laboratories to determine whether or not the organic fraction was necessary for the rat's response to diesel soot. Heinrich et al. (1995) exposed rats in parallel to diesel soot, mutagen-poor carbon black, and fine titanium dioxide particles. Nikula et al. (1995) exposed rats in parallel to diesel soot and a different mutagen-poor carbon black. Although the studies were designed differently, they yielded the same conclusion. Both studies demonstrated that the lung tumor exposure-response relationships to diesel soot and carbon black were identical, and the study by Heinrich et al. also produced an identical response to titanium dioxide. These findings indicate that the organic fraction of diesel soot played no significant role in its carcinogenicity in rats. This finding indicates that the rat lung tumor response to diesel soot is not relevant to carcinogenic hazard or lung cancer risk from the soot-associated organic mutagens.

Current Understanding of Human Lung Cancer Risk

Epidemiology

Rat Lung Tumor Data

Numerous estimates of human lung cancer risk have been derived from the rat lung tumor data since the first results became known in the mid-1980s. Since that time, the evidence against using the rat data, reviewed above, has accumulated progressively. At this time, there appears to be no scientific basis for using the rat lung tumor data to either infer the existence of human lung cancer risk or to make estimates of its magnitude.

Comparative Mutagenic Potency

Summary of Current Understanding of Lung Cancer Risk

Changes in Respiratory Function and Structure

Experimental Exposures of Humans

Epidemiological Studies of Humans

Effects from a Single Workshift

Longer-Term Effects

Animal Studies

There is little additional information on the effects of inhaled diesel exhaust on respiratory function and lung structure of animals beyond that reviewed previously (Mauderly 1994a,b, 1996; HEI 1995). The largest body of information is derived from studies of rodents, and reflects the species differences discussed briefly in the preceding section on lung cancer. Near lifetime repeated exposures of rats at concentrations of soot over approximately 1 mg/m^3 overwhelms the ability of normal particle clearance pathways and results in a progressive accumulation of soot in the lung. This accumulation is accompanied by persistent inflammation, focal epithelial proliferation and metaplasia, and fibrosis (Mauderly 1996). The progressive structural changes are reflected by a progressive impairment of respiratory function which includes lung stiffening (loss of compliance), reduced lung volumes, uneven intrapulmonary gas distribution, and impaired alveolar-capillary gas exchange (Mauderly et al. 1988). This structure-function syndrome also occurs in rats exposed heavily to other solid, respirable particles (Mauderly 1994b). Of importance from a human exposure viewpoint, no significant alterations of particle clearance (Wolff et al. 1987), inflammation, fibrosis (Henderson et al. 1988) or respiratory function or structure (Mauderly et al. 1988) resulted from chronic exposures of rats at $350 \text{ } \mu\text{g soot/m}^3$, even though small amounts of soot accumulated in the lungs. Under identical exposure conditions, mice accumulate similar amounts of soot in their lungs (Henderson et al. 1988), but the inflammatory, fibrotic (Henderson et al. 1988) and histopathological (Mauderly et al. 1996) responses are less than those in rats. Small reductions in lung volumes and compliance have also been observed in diesel-exposed Syrian (Heinrich et al. 1986) and Chinese (Vinegar et al. 1981) hamsters. Mice and hamsters have also been shown to have lesser functional and structural responses than rats to other solid respirable particles (Mauderly 1994b).

A smaller, but perhaps more relevant, body of information comes from nonrodent species which have respiratory bronchioles (absent in rodents) and other lung features more similar to humans. Only two species have been chronically exposed to diesel exhaust. The U.S. EPA exposed male cats chronically to exhaust at 6 mg soot/m^3 for 61 weeks, and then at 12 mg/m^3 for the remainder of 27 months, followed by a 6 month recovery period (Pepelko and Peirano 1983). A restrictive functional impairment with decreased lung volumes and uneven intrapulmonary gas distribution was observed at the end of the exposure (Moorman et al. 1985). Histopathology at the end of exposure included peribronchiolar fibrosis and epithelial metaplasia in terminal and respiratory bronchioles (Plopper et al. 1983). Interestingly, while the epithelial changes lessened

during the 6 month recovery period, the fibrosis progressed. Lewis et al. (1989) exposed cynomolgus monkeys to diesel exhaust at 2 mg soot/m³ and reported that the forced expiratory flow rates were reduced at the end of exposure (Lewis et al. 1986). The lung histopathology of the monkeys differed from that of rats exposed concurrently (Nikula et al. 1997). Soot was present in approximately the same tissue concentration in both species, but was located predominantly in interstitial compartments in monkeys and in alveolar lumens in rats. The species had similar increases in pulmonary macrophages. The most striking difference was in the degree of epithelial proliferation, which was characteristically prevalent near accumulations of soot in rats, but essentially absent in monkeys. Although the data base is small, these results suggest that nonrodent species can develop fibrosis and epithelial responses under extreme exposure conditions, but exhibit little structural response from chronic exposures at 2 mg soot/m³.

Asthma and Allergic Rhinitis

Nonpulmonary Health Effects

Bladder Cancer

Experimental Evidence for Other Nonpulmonary Effects

As predicted for man, rodents exposed chronically to diesel exhaust would be expected to ingest more soot than is deposited and retained in the lung by inhalation. This route of exposure results largely from the grooming habits of rodents, which cause the ingestion of soot deposited on the fur. Wolff et al. (1982) examined the gastrointestinal tract intake of gallium oxide particles in rats exposed repeatedly by either nose-only or whole-body methods. They estimated that the intake was approximately 60% greater in rats exposed whole-body than in those exposed nose-only and attributed this difference to grooming. Because the size and morphological characteristics of the gallium oxide particles were similar to those of diesel soot, this result suggests that animals in the diesel exhaust studies listed in Tables 5-4 and 5-5 ingested substantial amounts of soot. These studies, therefore, constitute a reasonable examination of the hazard associated with ingestion and absorption of diesel exhaust vapors and soot-associated chemicals. Few of the reports of animal studies, however, gave detailed information on nonpulmonary health effects.

Nonpulmonary Cancer

Specific information on cancer in organs other than the respiratory tract was reported only for four studies of rats and one study of hamsters included in Tables 8-4 and 8-5. Karagianes et al. (1981) reported that no significant exposure-related lesions were found in the esophagus or stomach of rats. Kaplan et al. (1983) reported that no lesions were found in tissues other than the respiratory system of rats (and hamsters) that could be attributed to exposure. Ishihara (1988) reported that there were no differences between exposed and control rats in the incidences of leukemia, Leydig cell tumors, mammary gland tumors, or total nonpulmonary tumors. Lewis et al. (1989) examined 50

organs and gave detailed data for tumors in 11 nonpulmonary organs, including the bladder. They found no exposure-related difference in nonpulmonary carcinogenesis.

Although other reports did not detail non-lung findings, many studies (e.g., Heinrich et al. 1986; Mauderly et al. 1987; Nikula et al. 1995) included complete necropsies of all animals, which involved gross observations of all major organs. From published information and personal communications, it is evident that no increased incidence of non-lung cancers was observed in any of these studies.

Noncancer Effects

Three reports included information on noncancer, nonpulmonary health effects of chronic diesel exhaust exposures of animals. Among the variety of health endpoints that were evaluated, no consistent pattern of effects emerged; thus, these reports are not reviewed in detail here. Only some of the results are mentioned below; the reader is referred to the original reports for details.

Pepelko and Peirano (1983) reported results of a series of studies that included exposures of fruit flies, mice, hamsters, rats, rabbits, and cats. These authors investigated a spectrum of nonpulmonary endpoints including spermatogenesis, heritable mutations, hematopoiesis, hematology, serum chemistry, xenobiotic-metabolizing enzymes, and neurophysiology, and the reader is referred to the report for details. Few significant exposure-related differences were observed. The learning ability of rats exposed soon after birth was reported to have been impaired. An increase in the fraction of banded neutrophils was found in the circulating blood of male cats exposed for 12 months to exhaust at 6 mg soot/m³.

Ishihara (1988) evaluated hematology, serum chemistry, and hematopoiesis in rats and mice exposed chronically. Hematopoiesis was unaffected in mice or rats. Elevations in circulating erythrocyte concentrations with reduced cell volume and hemoglobin concentration occurred in exposed rats. Several modest changes in serum chemistry were observed in rats, and these were resolved after cessation of exposure.

Lewis et al. (1989) exposed mice, rats, and monkeys chronically to diesel exhaust and, evaluated hematopoiesis, hematology, serum chemistry, splenic lymphocyte blast transformation, spermatogenesis, and xenobiotic metabolic enzymes in liver. The fraction of banded circulating neutrophils was increased in rats, but few other exposure-related differences were observed.

The results of these studies indicate that, other than modest alterations in hematology and serum chemistry, few nonpulmonary health effects are observed in animals exposed chronically to high concentrations of diesel exhaust. The experimental evidence, therefore, does not support concern for nonpulmonary effects.

CURRENT ISSUES AND RESEARCH NEEDS

Lung Cancer Risk From Environmental and Occupational Exposures

Measurement of Human Exposures to Diesel Exhaust

Bioavailability and Bioactivity of Diesel Soot-Associated Organic Mutagens

Impact on Health Risk of Reduced Soot Particle Size

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REFERENCES

- Cal EPA (California Environmental Protection Agency). 1997. *Health Risk Assessment for Diesel Exhaust*. Office of Environmental Health Hazard Assessment.
- CASAC (Clean Air Scientific Advisory Committee). 1995. *Health Assessment Document for Diesel Emissions*. EPA-SAB-CASAC-95-XXX.
- Cross, E T., R. E Palmer, R. E. Filipy, R. H. Busch, and B. O. Stuart. 1978. *Study of the Combined Effects of Smoking and Inhalation of Uranium Ore Dust, Radon Daughters, and Diesel Exhaust Fumes in Hamsters and Dogs*. Report No. PNL-2744: UC-48. Richland, WA: Pacific Northwest Laboratory.
- EPA (U.S. Environmental Protection Agency). 1993. *Motor Vehicle-Related Air Toxics Study*. EPA 420-R-93-005. Ann Arbor, MI: Office of Mobile Sources, Emission Planning and Strategies Division.
- EPA (U.S. Environmental Protection Agency). 1994. *Health Assessment Document for Diesel Emissions, Volumes I and II*. EPA/600/8-90/057Ba. Washington, DC: Office of Research and Development.
- HEI (Health Effects Institute). 1995. *Diesel Exhaust: A Critical Analysis of Emissions, Exposure, and Health Effects. A Special Report of the Institute's Diesel Working Group*. Cambridge, MD: Health Effects Institute.
- Heinrich, U., L. Peters, W. Funcke, E. Potts, U. Mohr, and W. Stöber. 1982. Investigations of toxic and carcinogenic effects of diesel exhaust in long-term inhalation exposure of rodents. In *Toxicological Effects of Emissions from Diesel Engines*, ed. J. Lewtas, pp.225-42. Amsterdam: Elsevier.
- Heinrich, U., H. Muhle, S. Takenaka, E. Ernst, R. Fuhst, U. Mohr, E Pott, and W. Stöber. 1986. Chronic effects on the respiratory tract of hamsters, mice and rats after long-term inhalation of high concentrations of filtered and unfiltered diesel engine emissions. *J. Appl. Toxicol.* 6:383-95.
- Heinrich, U., R. Fuhst, S. Rittinghausen, O. Creutzenberg, B. Bellmann, W. Koch, and K. Levsen. 1995. Chronic inhalation exposure of Wistar rats and two different strains of mice to diesel engine exhaust, carbon black, and titanium dioxide. *Inhal. Toxicol.* 7:533-56.

- Henderson, R. F., J. A. Pickrell, R. K. Jones, J. D. Sun, J. M. Benson, J. L. Mauderly, and R. O. McClellan. 1988. Response of rodents to inhaled diluted diesel exhaust: Biochemical and cytological changes in bronchoalveolar lavage fluid and in lung tissue. *Fundam. Appl. Toxicol.* 11:546-67.
- Ishihara, T. 1988. *Diesel Exhaust and Health Risks. Final Report of HERP Studies.* Tsukuba, Japan: Health Effects Research Program.
- Ishinishi, N., A. Koizumi, R. O. McClellan, and W. Stöber. 1986a. *Carcinogenic and Mutagenic Effects of Diesel Engine Exhaust.* Amsterdam: Elsevier.
- Kaplan, H. L., K. J. Springer, and W. F. MacKenzie. 1983. *Studies of Potential Health Effects of Long-Term Exposure to Diesel Exhaust Emissions. Final Report No. 01-0750-103 (SWRI) and No. 1239 (SFRE).* San Antonio, TX: Southwest Research Institute.
- Karagianes, M. T., R. F. Palmer, and R. H. Busch. 1981. Effects of inhaled diesel emissions and coal dust in rats. *Am. Ind. Hyg. Assoc. J.* 42:382-91.
- Kotin, P., H. L. Falk, and M. Thomas. 1955. Aromatic hydrocarbons: III. Presence in the particulate phase of diesel-engine exhausts and the carcinogenicity of exhaust extracts. *Arch. Ind. Health* 11:113-20.
- Lewis, T. R., F. H. Y. Green, W. J. Moorman, J. A. R. Burg, and D. W. Lynch. 1986. A chronic inhalation toxicity study of diesel engine emissions and coal dust, alone and combined. In *Carcinogenic and Mutagenic Effects of Diesel Engine Exhaust*, eds. N. Ishinishi, A. Koizumi, R. O. McClellan, and W. Stöber, pp. 361-80. Amsterdam: Elsevier.
- Lewis, T. R., F. H. Y. Green, W. J. Moorman, J. R. Burg, and D. W. Lynch. 1989. A chronic inhalation toxicity study of diesel engine emissions and coal dust, alone and combined. *J. Am. Coll. Toxicol.* 8:345-75.
- Mauderly, J. L. 1992. Diesel exhaust. In *Environmental Toxicants—Human Exposures and Their Health Effects*, ed. M. Lippmann, pp. 119-62. New York, NY: Van Nostrand Reinhold.
- Mauderly, J. L. 1994a. Toxicological and epidemiological evidence for health risks from inhaled engine emissions. *Environ. Health Perspect.* 102(Suppl. 4):165-71.
- Mauderly, J. L. 1994b. Non-cancer pulmonary effects of chronic inhalation exposure of animals to solid particles. In *Toxic and Carcinogenic Effects of Solid Particles in the Respiratory Tract*, eds. U. Mohr, D. L. Dungworth, J. L. Mauderly, and G. Oberdoerster, pp. 43-56. Washington, DC: ILSI Press.
- Mauderly, J. L. 1996. Lung overload: The dilemma and opportunities for resolution. *Inhal. Toxicol.* 8(Suppl.):1-28.
- Mauderly, J. L. 1997a. Toxicology of diesel engine emissions. *J. Air Waste Manag. Assoc.* (submitted).
- Mauderly, J. L. 1997b. Relevance of particle-induced rat lung tumors for assessing lung carcinogenic hazard and human lung cancer risk. *Environ. Health Perspect.* 105(Suppl. 5):1337-46.
- Mauderly, J. L., and McCunney. 1996. *Particle Overload in the Rat Lung and Lung Cancer: Implications for Human Risk Assessment.* Washington, DC: Taylor & Francis.

- Mauderly, J. L., E. B. Barr, D. E. Bice, A. F. Eidson, R. F. Henderson, R. K. Jones, J. A. Pickrell, and R. K. Wolff. 1986. Inhalation exposure of rats to oil shale dust and diesel exhaust. In *Inhalation Toxicology Research Institute Annual Report, DOE Research and Development Report LMF-115*, pp. 273-78. Springfield, VA: National Technical Information Service.
- Mauderly, J. L., R. K. Jones, W. C. Griffith, R. F. Henderson, and R. O. McClellan. 1987. Diesel exhaust is a pulmonary carcinogen in rats exposed chronically by inhalation. *Fundam. Appl. Toxicol.* 9:208-21.
- Mauderly, J. L., N. A. Gillett, R. F. Henderson, R. K. Jones, and R. O. McClellan. 1988. Relationships of lung structural and functional changes to accumulation of diesel exhaust particles. *Ann. Occup. Hyg.* 32(Suppl. 1):659-69.
- Mauderly, J. L., D. E. Bice, Y. S. Cheng, N. A. Gillett, W. C. Griffith, R. F. Henderson, J. A. Pickrell, and R. K. Wolff. 1990a. Influence of pre-existing pulmonary emphysema on susceptibility to chronic inhalation exposure to diesel exhaust. *Am. Rev. Respir. Dis.* 141:1333-41.
- Mauderly, J. L., Y. S. Cheng, and M. B. Snipes. 1990b. Particle overload in toxicological studies: Friend or foe? *J. Aerosol Med.* 3:S-169-87.
- Mauderly, J. L., D. A. Banas, W. C. Griffith, F. F. Hahn, R. F. Henderson, and R. O. McClellan. 1996. Diesel exhaust is not a pulmonary carcinogen in CD-1 mice exposed under conditions carcinogenic to F344 rats. *Fundam. Appl. Toxicol.* 30:233-42.
- McClellan, R. O. 1996. Lung cancer in rats from prolonged exposure to high concentrations of carbonaceous particles: Implications for human risk assessment. *Inhal. Toxicol.* 8(Suppl.):193-226.
- Moorman, W. J., J. C. Clark, W. E. Pepelko, and J. Mattox. 1985. Pulmonary function responses in cats following long-term exposure to diesel exhaust. *J. Appl. Toxicol.* 5:301-5.
- Nikula, K. J., M. B. Snipes, E. B. Barr, W. C. Griffith, R. F. Henderson, and J. L. Mauderly. 1995. Comparative pulmonary toxicities and carcinogenicities of chronically inhaled diesel exhaust and carbon black in F344 rats. *Fundam. Appl. Toxicol.* 25:80-94.
- Nikula, K. J., W. C. Griffith, K. J. Avila, and J. L. Mauderly. 1997. Lung tissue responses and site of particle retention differ between rats and Cynomolgus monkeys exposed chronically to diesel exhaust and coal dust. *Fundam. Appl. Toxicol.* 37:37-53.
- Pepelko, W. E., and W. B. Peirano. 1983. Health effects of exposure to diesel engine emissions. A summary of animal studies conducted by the US Environmental Protection Agency's Health Effects Research Laboratory at Cincinnati, OH. *J. Am. Coll. Toxicol.* 2:253-306.
- Plopper, C. G., D. M. Hyde, and A. J. Weir. 1983. Centriacinar alterations in lungs of cats chronically exposed to diesel exhaust. *Lab. Invest.* 49:391-99.
- Takemoto, K., H. Yoshimura, and H. Katayama. 1986. Effects of chronic inhalation exposure to diesel exhaust on the development of lung tumors in di-isopropanol-nitrosamine-treated F344 rats and newborn C57BL and ICR mice. In *Carcinogenic and Mutagenic Effects of Diesel Engine Exhaust*, eds. N. Ishinishi, A. Koizumi, R. O. McClellan, and W. Stöber, pp. 311-27. Amsterdam: Elsevier.

- Vinegar, A., A. I. Carson, W. E. Pepelko, and J. G. Orthoefer. 1981. Effects of six months of exposure to two levels of diesel exhaust on pulmonary function of Chinese hamsters (abstract). *Fed. Proc.* 40:593.
- Wolff, R. K., L. C. Griffis, C. H. Hobbs, and R. O. McClellan. 1982. Deposition and Retention of $0.1 \mu\text{m}^{67}\text{Ga}_2\text{O}_3$ aggregate aerosols in rats following whole body exposures. *Fundam. Appl. Toxicol.* 126:505-8.
- Wolff, R. K., R. F. Henderson, M. B. Snipes, W. C. Griffith, J. L. Mauderly, R. G. Cuddihy, and R. O. McClellan. 1987. Alterations in particle accumulation and clearance in lungs of rats chronically exposed to diesel exhaust. *Fundam. Appl. Toxicol.* 9:154-66.

TABLE 8-4. Studies of Lung Cancer in Rats Exposed Chronically to Whole Diesel Exhaust

Date	Author	Strain	Sex	Animals		Exposure				Lung Tumors			
				Age at Start (weeks)	Number per Group ^a	Engine	Operating Mode	Hours/Day x Days/Week	Months	Soot Concentration (mg/m ³)	Percentage with Tumors	<i>p</i> < 0.05	
1981	Karagianes et al.	Wistar	M	18	6	3-cyl, 43-hp electrical generator	Variable speed and load	6 x 5	20	0	0	0	-
1983	Kaplan et al.	F344	M	8	30	Oldsmobile 5.7 L	Constant speed	20 x 7	15 (8) ^b	0	0	16.7	-
1983	White et al.									0.25	3.3	NR ^c	
										0.75	10.0	NR	
										1.5	3.3	NR	
1986	Heinrich et al.	Wistar	F	8-10	96	Volkswagen 1.6 L	Variable, U.S. FTP ^d	19 x 5	32	0	0	0	+
1986	Iwai et al.	F344	F	7	24	2.4-L truck engine	Constant speed	8 x 7	24 (6)	0	4.5	15.8	+
1986	Takemoto et al.	F344	F	5	15	Yanmar 0.27 L	Constant idle	4 x 4	24	0	4.9	42.1	+
1987	Mauderly et al.	F344	M+F	17	220	Oldsmobile 5.7 L	Variable, U.S. FTP	7 x 5	30	0	0	0	-
										0.35	0.9	0.9	
										3.5	1.3	3.6	+
										7.1	12.8	12.8	+
1988	Ishihara	F344	M+F	5	123	1.8-L 4-cyl, light duty	Constant speed	16 x 6	30	0	0	3.3	-
										0.1	2.4	2.4	-
										0.4	0.8	0.8	-
										1.1	4.1	4.1	-
										2.3	2.4	2.4	-

^aNumber of rats examined for lung tumors.

^bValue in parentheses is number of months rats were observed after cessation of exposure

^cNR = not reported.

^dFTP = Federal Test Procedure, EPA urban certification cycle (US-72).

(continued)

TABLE 8-4. (Concluded)

Date	Author	Strain	Sex	Animals		Exposure					Lung Tumors		
				Age at Start (weeks)	Number per Group ^a	Engine	Operating Mode	Hours/Day x Days/Week	Months	Soot Concentration (mg/m ³)	Percentage with Tumors	p < 0.05	
1988	Ishihara	F344	M+F	5	123	11-L, 6 cyl, heavy duty	Constant speed	16 x 6	30	0	0.8	0.8	-
										0.5	0.8	0.8	-
										1.0	0	0	-
										1.8	3.3	3.3	-
										3.7	6.5	6.5	+
1989	Brightwell et al.	F344	M+F	6-8	144	Volkswagen 1.5 L	Variable, U.S. FTP	16 x 5	24 (6)	0	1.2	1.2	-
										0.7	0.7	0.7	-
										2.2	9.7	9.7	+
										6.6	38.5	38.5	+
1989	Lewis et al.	F344	M+F	(Weanling)	180	3304 Caterpillar 7.0 L with water scrubber	Variable, mine cycle	7 x 5	24	0	3.3	3.3	-
										1.95	4.4	4.4	-
1990a	Mauderly et al.	F344	M	18	34	Oldsmobile 5.7 L	Variable, U.S. FTP	7 x 5	24	0	0	0	-
										3.5	2.9	2.9	-
1990b	Mauderly et al.	F344	M+F	19	80	Oldsmobile 5.7 L	Variable, U.S. FTP	7 x 5	30	0	0	0	+
										3.5	6.5	6.5	+
1995	Heinrich et al.	Wistar	F	7	100-200	Volkswagen 1.6 L	U.S. FTP	18 x 5	24 (6)	0	0.5	0.5	-
										0.8	0	0	-
										2.5	2.0	2.0	-
										7.0	9.0	9.0	+
1995	Nikula et al.	F344	M+F	7-9	210-214	GMLH6 6.2 L	U.S. FTP	16 x 5	24	0	1.4	1.4	+
										2.4	6.2	6.2	+
										6.3	17.9	17.9	+

TABLE 8-5. Studies of Lung Cancer in Mice and Syrian Hamsters Exposed Chronically to Whole Diesel Exhaust

Date	Author	Animals				Exposure				Lung Tumors		
		Strain	Sex	Age at Start (weeks)	No. per Group ^a	Engine	Operating Mode	Hours/Day x Days/Week	Months	Soot Concentration (mg/m ³)	Percentage with Tumors	p < 0.05
<i>Mice</i>												
1983	Pepelko and Peirano	Strong-A	F	6	56-58	Nissan 3.2 L	Variable, Federal short cycle	8 x 7	7.5	0 6.0	6.9 25.0	+
		Strong-A	M	6	368-403	Nissan 3.2 L	Variable, Federal short cycle	8 x 7	7.5	0 6.0	18.1 17.9	-
		Strong-A	M+F	6	80-87	Nissan 3.2 L	Variable, Federal short cycle	8 x 7	7.5	0 12.0	24.1 12.5	+
		Strong-A	M+F	6	237-250	Nissan 3.2 L	Variable, Federal short cycle	8 x 7 (dark) ^b	7.5	0 12.0	24.9 8.8	+
		Jackson-A	M	6	38-44	Nissan 3.2 L	Variable, Federal short cycle	8 x 7	10.5	0 12.0	57.9 25.0	+
		Sencar	F	in utero ^c	104-111	Nissan 3.2 L	Variable, Federal short cycle	8 x 7	1.5	0 6/12 ^d	7.2 16.3	+
		Sencar	M	in utero ^e	101-105	Nissan 3.2 L	Variable, Federal short cycle	8 x 7	1.5	0 6/12 ^d	3.8 5.9	+

^aNumber examined for lung tumors.

^bLight cycle altered for exposure during dark period.

^cParents mated and offspring born in exposure atmospheres.

^dExposed to 6 mg/m³ to 12 weeks of age, then to 12 mg/m³.

^eNR = not reported.

^fMaximum possible exposure was 28 months, longest exposure of hamsters not reported.

^gExposures at 0.7 and 2.2 mg/m³ were also conducted, but detailed tumor results were not published.

^hValue in parentheses is number of months mice were observed after cessation of exposure.

(continued)

TABLE 8-5. (Continued)

Date	Author	Strain	Sex	Animals		Exposure				Lung Tumors		
				Age at Start (weeks)	No. per Group ^a	Engine	Operating Mode	Hours/Day x Days/Week	Months	Soot Concentration (mg/m ³)	Percentage with Tumors	p < 0.05
1983	Kaplan et al.	Jackson-A	M	8	388-399	Oldsmobile 5.7 L	Constant speed	20 x 7	8	0	33.5	-
										0.25	33.8	-
										0.75	27.3	-
										1.50	25.0	+
1986	Heinrich et al.	NMRI	F	8-10	84-93	Volkswagen 1.6 L	Variable, U.S. FTP	19 x 5	28	0	13.0	+
										4.2	32.0	+
1986	Takemoto et al.	C57BL/6N	M+F	Birth	59-188	Yanmar 0.27 L	Constant idle	4 x 4	28	0	1.7	NR ^b
										2-4	9.0	NR ^b
										0	7.3	NR
										2-4	13.3	NR
1995	Heinrich et al.	C57BL/6N	F	7	120	Volkswagen 1.6 L	U.S. FTP	18 x 5	24	0	5.1	-
										4.5	8.5	-
										0	30.0	-
										4.5	23.0	-
										0	30.0	-
										7.0	32.1	-
1996	Mauderly et al.	CD-1	M+F	16-18	155-186	Oldsmobile 5.7 L	U.S. FTP	7 x 5	24	0	13.4	-
										0.35	14.6	-
										3.5	9.7	-
										7.1	7.5	-
<i>Syrian Hamsters</i>												
1978	Cross et al.	Syrian golden	M	12	102	3 cyl, 43 hp electrical generator	Variable speed and load	6 x 5	20	0	0	0
										7.3	0	0
1982	Heinrich et al.	Syrian golden	F	8	48	Daimler-Benz 2.4 L	Constant speed and load	7-8 x 5	24	0	0	0
										3.9	0	0

(continued)

TABLE 8-5. (Concluded)

Date	Author	Animals			Exposure				Lung Tumors			
		Strain	Sex	Age at Start (weeks)	No. per Group ^a	Engine	Operating Mode	Hours/Day × Days/Week	Months	Soot Concentration (mg/m ³)	Percentage with Tumors	<i>p</i> < 0.05
1983	Kaplan et al.	Syrian golden	M	8	30	Oldsmobile 5.7 L	Constant speed	20 × 7	15	0	0	0
										0.25	0	0
										0.75	0	0
										1.50	0	0
1986	Heinrich et al.	Syrian golden	M+F	8-10	96	Volkswagen 1.6 L	Variable, U.S. FTP	19 × 5	Lifetime ^f	0	0	0
										4.2	0	0
1989	Brightwell et al.	Syrian golden	M+F	6-8	203-410	Volkswagen 1.5 L	Variable, U.S. FTP	16 × 5	24	0	0.2	0
										6.6 ^g	0	0

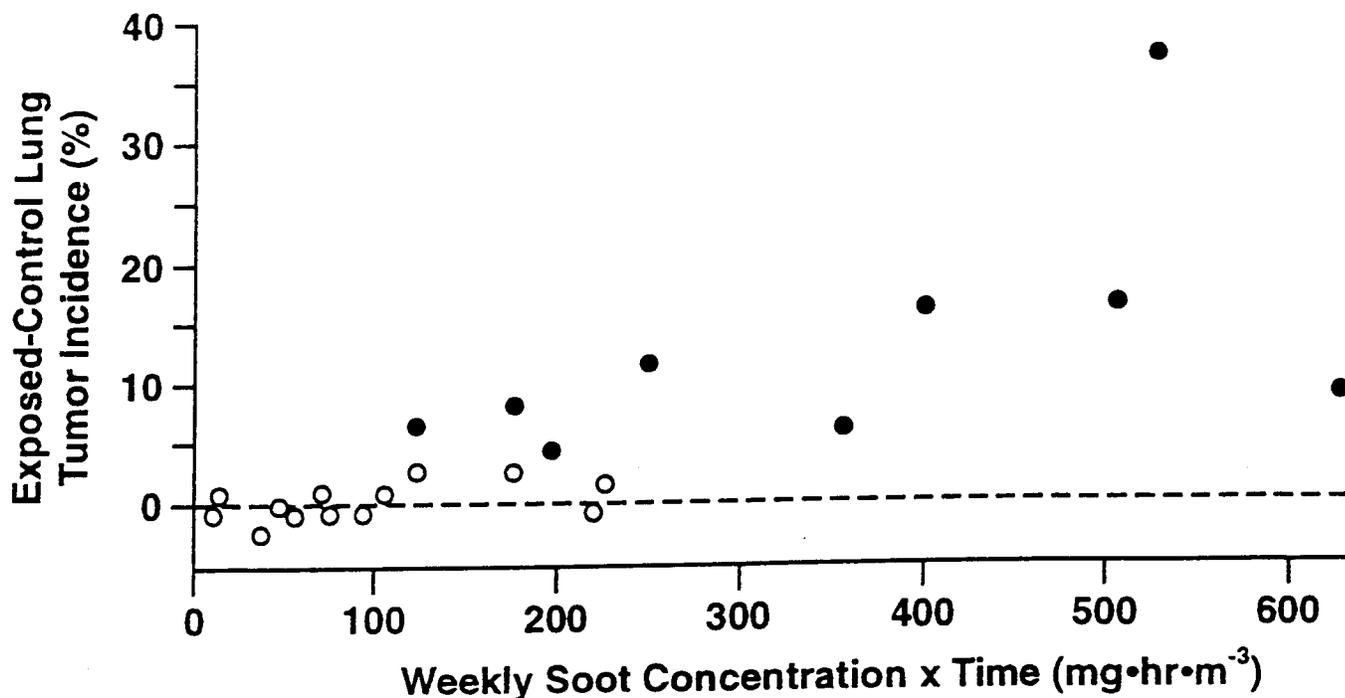


Figure 8-1. The relationship between diesel exhaust exposure and the rat lung tumor response is illustrated by aggregate data from the eight published studies including groups of 50 or more rats and exposures of 24 months or longer (Heinrich et al. 1986; Mauderly et al. 1987; Ishihara 1988; Brightwell et al. 1989; Lewis et al. 1989; Mauderly et al. 1990b; Heinrich et al. 1995; Nikula et al. 1995). The lung tumor response is expressed as the net (exposed minus control) lung tumor incidence, and the dashed line represents the control incidence (no net increase) for each study. Because all studies used weekly repeating exposure patterns, exposures are normalized by expression as the weekly exposure rate (mg/m^3 times hours per week). Filled circles represent treatment groups with statistically significant increases above individual study control tumor incidences, and open circles represent exposed groups with no increase or statistically insignificant increases above the control incidences. The aggregate results indicate a response threshold. Exposure rates of $106 \text{ mg}^3 \cdot \text{hr}^3 \cdot \text{m}^{-3}$ or below produced no suggestion of a tumor response among nine groups including a total of 1359 rats exposed at five laboratories in four countries.

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Relation Between Exposure to Diesel Emissions and Dose to the Lung

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Private Consultant

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received

animal species (Mauderly et al. 1987; see also Oberdörster and Pepelko 1992 and Oberdörster 1994). For example, Henderson and coworkers (1988) reported that with identical exposure regimens, mice accumulated a greater lung burden of diesel exhaust particles than rats; however, some cellular responses, such as fibrotic lesions, were greater in rats. Mauderly and coworkers (1987) also showed that after six months of exposure, developing rats had lung burdens of diesel exhaust particles (as expressed in mg/g of lung tissue) similar to lung burdens in adult animals; however, toxic effects were less severe in the developing animals.

In summary, alveolar deposition of fine particles, such as diesel soot, is relatively unaffected by species or by previous exposure. Clearance, however, differs across species and is retarded by previous particle burden (Morrow et al. 1991). In chronic exposure at milligram concentrations, clearance is retarded by a high dose rate (Bellmann et al. 1983), whereas at microgram levels, clearance is more efficient with high dose rates (Strom et al. 1990). Thus retention, which varies inversely with rate of clearance, differs across species, is greater in previously or simultaneously exposed lungs (possibly above an identifiable lung burden), and may be a principal variable in risk assessment considerations. Although lung burden, or some resultant biologic effect, may be a quantitative indicator of dose, the important biologic variable is clearance, because it determines retention and lung burden. The structural, biophysical, and functional properties that determine its efficiency, however, need clarification.

PARTICLE-ASSOCIATED ORGANIC COMPOUNDS

Diesel exhaust is inhaled as a complex physicochemical mixture of organic aerosols, vapor-phase organic and inorganic compounds, and particle-adsorbed materials. The particles and their composite materials distribute along the bronchoalveolar tract according to size, as discussed above. The polar and water-soluble gases tend to be removed in the nasal passages and the proximal bronchi. Reactive oxidants interact maximally at the bronchoalveolar junction. The organic compounds may be desorbed by the lipids of the alveolar lining layer and possibly into the intracellular fluids of the phagocytic cells. As the phagocytizing macrophages move through the lungs, the dosage of the different chemicals may be delivered at different points along the respiratory tract and at different rates to the bronchoalveolar fluids, the underlying cells, and the lymphatic and blood circulations. The extent to which organic compounds desorb from the particles determines their bioavailability for subsequent reactions with cellular molecules such as DNA.

The critical factors in the bioavailability of the active mutagenic polycyclic aromatic hydrocarbons (PAHs)* of the diesel particle are (1) the surface structure of the particle, (2) the composition of the adsorbed organic compounds, (3) the composition of the extracellular and intracellular fluids, (4) the balance of the molecular binding forces between the particle and the adsorbed organic molecules, on the one hand, and the extracting biologic fluids on the other, and (5) the metabolism of the desorbed chemical. The physicochemical properties of the vapor-particle linkage, such as molecular binding energies, probably determine the bioavailability of the organic chemical at the site of deposition of diesel exhaust particles in the bronchioles and alveoli (Gerde et al. 1991).

The structure of the diesel exhaust particle is described in the background paper by Sawyer and Johnson in this report. Briefly, the particle is a chain and cluster of carbonaceous aggregates, with PAHs adsorbed on the surfaces of the interstices. Adsorbed organic compounds may not be readily bioavailable because of high binding energies, which prevent the release of the compounds to the cell. In general, organic vapor molecules occupy the tightest binding sites

* A list of abbreviations appears at the end of this paper.

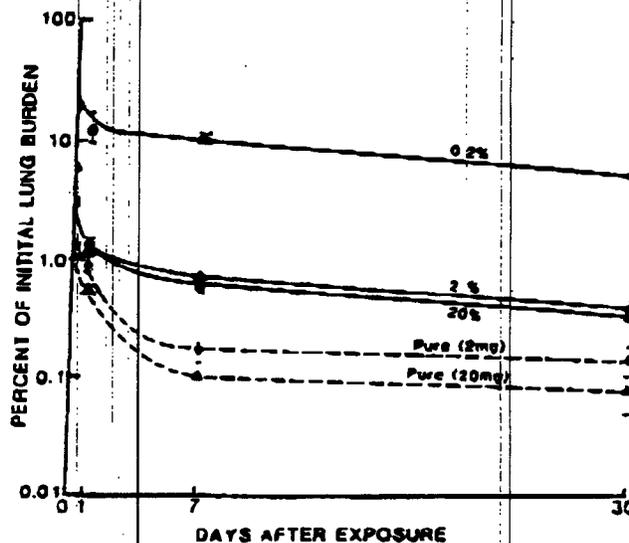


Figure 5. Lung clearance of ¹⁴C following nose-only inhalation exposure of rats to aerosols of pure [¹⁴C]BaP (2 or 20 mg/m³) or [¹⁴C]BaP adsorbed onto carbon black particles at 0.2%, 2.0%, or 20% by mass (total particle concentration = 79–100 mg/m³). As a function of time, retention values are expressed as percentages of the calculated initial deposition of ¹⁴C in lungs based on a deposition value of 15% and a rate per minute volume of 0.20 L/min. Values are means ± SE. (From Sun JD, Wolf RK, Maio SM, Barr EB, 1989, Inhalation Toxicol 1(1):10, Taylor and Francis, Inc., Washington, DC. Reproduced with permission. All rights reserved.)

(greatest binding energies) on the particle first, and then remaining molecules occupy sites with lower binding energies. Thus, when adsorbed onto particles at lower concentrations, organic compounds are more tightly bound than at higher concentrations. The studies of Sun and coworkers (1989) (Figure 5) support this point, showing much longer retention of benzo[a]pyrene (BaP) adsorbed onto carbon particles at low (0.2%) versus high (2.0% or 20%) concentrations. In contrast, particles consisting entirely of PAHs (Ebert 1990) may be far more bioavailable because no solid carbon core exists to exert binding energy and inhibit dissolution of the organic compounds into the lipid layers. The physicochemical behavior of the gas-particle relation is the critical factor in bioavailability.

An additional factor in the rate of release of potentially bioactive compounds is the degree of agglomeration of free and intracellular particles (Gerde et al. 1991), which occurs with tracheal instillation (Sun et al. 1989) and with inhalation at the high exposure levels used to produce lung tumors in animals. Agglomeration appears to retard the release of the organic compounds and to prolong the dose administration to the lung cells.

Compared with aerosols of pure organic compounds, adsorption of mutagenic organic compounds to diesel exhaust particles increases their deposition in the lungs and prolongs their retention and the time-course of their release (Creasia et al. 1976; Sun et al. 1983, 1984, 1989; Sun and McClellan 1984; Bond et al. 1986; Wolff et al. 1989) (Figure

6). Adsorption of volatile organic compounds to particles also increases postexposure covalent binding of the organic molecule to lung macromolecules (Figure 7).

The thickness of the respiratory tract fluid layer may be a significant factor in the rate at which chemicals are delivered to the underlying epithelium in the larger airways. The presence of lipid surfactant material in the alveoli, however, may delay the penetration of lipophilic deposits and allow surface flows to remove the chemicals before the penetration of material to underlying cells (Gerde and Scholander 1989).

Finally, the intracellular environment has a mitigating effect on the bioavailability and toxicity of adsorbed organic compounds. Phagocytosis of diesel particles by alveolar macrophages sharply reduces the mutagenicity of particles subsequently released from the cells (King et al. 1983; Bond et al. 1984). Phagocytosis also diminishes the quantity of extractable organic compounds, presumably by intracellular metabolism of the organic compounds. The mutagenicity of these organic compounds *in vivo* is significantly less than predicted from mutagenicity studies of chemically extracted material (Brooks et al. 1981; King et al. 1981; summarized by McClellan et al. 1982 and by Vostal 1983) (Figure 8). These data clearly show that extraction of particle-adsorbed organic compounds by relevant lung-based fluids is far less efficient than by chemical solvents (King et al. 1981). Furthermore, organic compounds extracted by biologic fluids simulating surfactant and respiratory tract fluids are dramatically less mutagenic in bacterial mu-

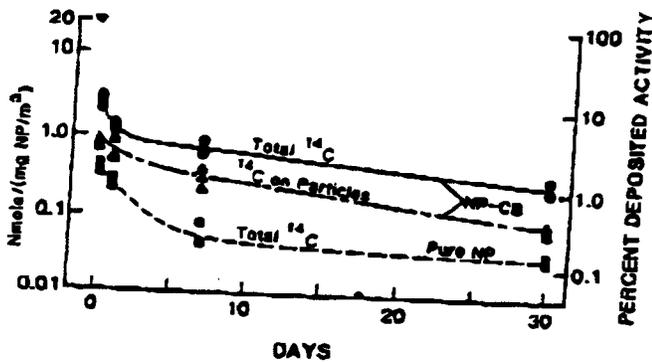


Figure 6. Lung retention of ^{14}C plotted as nitropryrene (NP) equivalents per milligram NP per cubic meter. Total ^{14}C in lung (●) and ^{14}C bound to particles (▲) are shown for rats exposed to NP adsorbed to carbon black particles. Total ^{14}C in lung (■) is shown for rats exposed to pure nitropryrene. Estimated initial deposited activity (▼) is shown for reference, and the axis on the right shows a scale calculated as the percentage of estimated initially deposited activity. The curves shown were calculated using best-fit two-component exponential functions. (From Wolff RK, Sun JD, Barr EB, Rutenberg SJ, Yeh HC, 1989. *J Toxicol Environ Health* 26:318. Taylor and Francis, Inc., Washington, DC. Reproduced with permission. All rights reserved.)

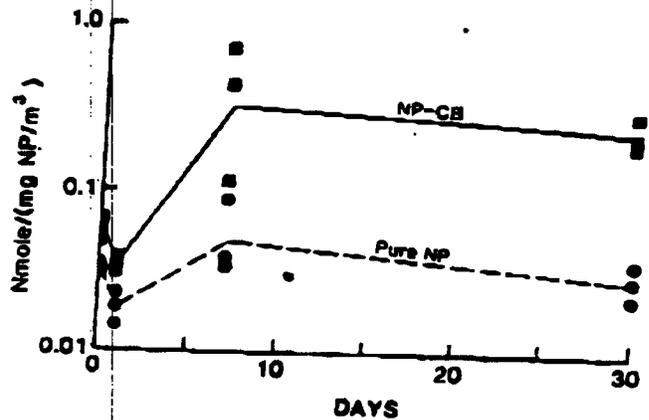


Figure 7. Activities of ^{14}C covalently bound to lung tissue plotted as nitropryrene (NP) equivalents per milligram NP per cubic meter for rats exposed to NP adsorbed to carbon black particles (■) and for rats exposed to pure NP aerosols (●). The lines shown join the means of the values at 7 days and 30 days (insufficient data to allow best-fit functions). (From Wolff RK, Sun JD, Barr EB, Rutenberg SJ, Yeh HC, 1989. *J Toxicol Environ Health* 26:319. Taylor and Francis, Inc., Washington, DC. Reproduced with permission. All rights reserved.)

agenicity test systems (Siak et al. 1980). These findings tend to diminish the role of particle-adsorbed mutagens in the pathogenesis of diesel-associated lung cancer.

In summary, adsorption of organic molecules to carbonaceous particles enhances their penetration into the respiratory portions of the lungs but diminishes their bioavailability in proportion to the binding energy of the organic molecules and the agglomeration of the particle. Organic compounds may be metabolized on the particle surface or after release, and may follow the particle in its pathway of clearance from the lungs. The effect of the biologic environment is to reduce the bioavailability of the particle-adsorbed organic compounds. The extracellular and intracellular environments are less able than chemical solvents to extract the organic compounds from the particle (probably because of weak nonpolar bonding), and the released organic compounds are less mutagenic than chemical extracts in bioassays.

RELATION OF PARTICLE LOCATION TO THE TOXICOLOGIC RESPONSE

One of the important factors in determining exposure-dose relationships to particle inhalation in the lung is the "moving target" characteristic of the migrating, particle-laden macrophage. If the particle dose is directly responsible for the subsequent pathology, then it is reasonable to expect a physical proximity of the particles and the pathology. If, however, the particle initiates a cascade of events that only distantly induces pathology, then geographic proximity is not necessary.

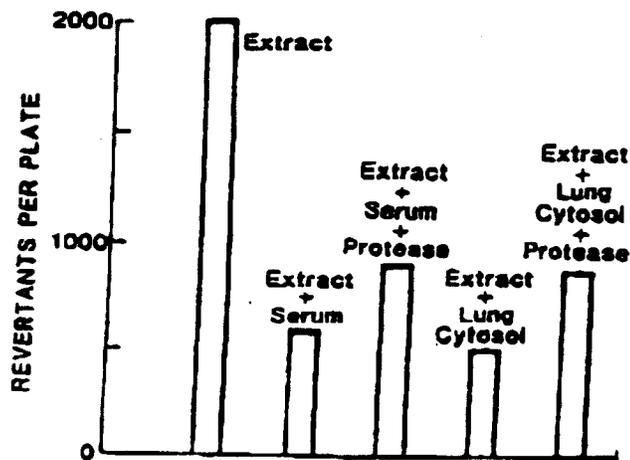


Figure 8. Influence of serum and lung cytosol on the mutagenicity of diesel exhaust particle extracts. (Reprinted with permission from Elsevier Service Publishing Co. and R.P. McClellan, as published in McClellan et al. 1982.)

Literature on the dynamic nature of particle movement, relative dose, and resultant toxicologic effect is particularly limited. After deposition and ingestion by macrophages, particles are variously transported either as free particles or within alveolar macrophages to the alveolar ducts and terminal bronchioles on their way to the mucociliary epithelia of the bronchioles; alternatively, particles may reach the local and regional lymphatics and be transported to peribronchial, perivascular, and subpleural sites of long-term storage. Although much of the understanding of intrapulmonary deposition and clearance has been obtained with carbon and other inert dusts (e.g., see Sorokin and Brain 1974), recent studies (Mauderly et al. 1986, 1994) indicate that diesel exhaust particles follow similar physiologic distributions. The level and precise cellular location of that dose may be critical to its ability to induce toxicity.

Well-documented studies of lung tumors induced by diesel exhaust have been performed by Mauderly and co-workers (1986, 1994) in rats. The tumors were located only in the peripheral lung, in contrast to the bronchial location of most human lung cancers. Diesel exhaust particles deposit and accumulate in the distal lung, and the associated cellular proliferation, inflammation, and hyperplasia take place at the alveolar and bronchiolar levels. Bond and coinvestigators (1988) showed that although the entire respiratory tract surface received exposure to the diesel exhaust particles, only the nasal turbinates and the peripheral lung, sites where particles are retained, showed an excessive level of DNA adducts. Thus these studies demonstrate a geographically quantitative relationship among concentration or duration of dose, biologic effect (adduct formation), and pathological effect.

EXPOSURE PARAMETERS AND THE DISTRIBUTION OF DOSE

The encounter between a hazardous agent and the host is termed exposure and has parameters pertaining to both the agent and the host. The encounter has time variables of duration, constancy or intermittency, frequency, and rate of delivery; the agent has properties of concentration and physicochemical state; the host brings structural and functional variables associated with state of activity, age, and disease. The interaction of these variables affects the distribution of effective dose in the lungs—that is, the proportional concentration of the agent on the respiratory membrane, in macrophages or epithelial cells, or at other sensitive sites depending on differences in deposition, transport, or cellular ingestion.

Time variables add to exposure, deposited and absorbed dose, and lung burden roughly in proportion to the total

in diesel exhaust is relatively unaffected by previous exposure. Clearance, however, declines with increasing dose and dose rate above a threshold. Since long-term dosimetry is determined by the differences between deposition and clearance, it can not be reliably extrapolated from acute to chronic exposures.

4. *Extrapolation from in vitro models to in vivo events.* Mathematical models provide "in vitro" data for dosimetry studies. These integrative models characterize the kinetics of deposition, clearance, and retention quite well for individual animal species and reasonably predict the deposition of diesel exhaust particles in humans. The models predict that lung clearance declines as continuous exposure concentrations rise from 100 to 1,000 $\mu\text{g}/\text{m}^3$. Intermittent exposure would increase by an order of magnitude the concentration of particles tolerated without clearance overload. Because human exposure to diesel exhaust under ambient conditions is intermittent and below these concentration levels (see the background paper by Watts, this report), it is unlikely to result in lung burdens sufficient to impair clearance, according to this model. The wide range of variation in clearance values between and within species, however, particularly in humans, renders extrapolation quite tenuous for lung burdens and associated health effects at a given exposure level without further experimental confirmation.

5. *Extrapolation of dose.* In experimental animals, clearance of diesel exhaust particles is maintained at continuous exposure levels in the 50 to 100 $\mu\text{g}/\text{m}^3$ range. In chronic exposure at high (milligram) concentrations, clearance is retarded by a high dose rate (Bellmann et al. 1983), whereas at low (microgram) levels, clearance is more efficient with high dose rates (Strom et al. 1990). Retention, which varies inversely with rate of clearance, is greater at high-dose than at low-dose rates. In addition, previous lung burden slows lung clearance, and there is a threshold for this effect (600 to 800 $\mu\text{g}/\text{g}$ of lung tissue in the rat). Thus retention increases with increasing dose and lung burden accumulates more rapidly as clearance fails. Since there appears to be a threshold for this effect, extrapolation of high-dose effects to low dose is unreliable.

6. *Extrapolation of mechanisms.* Adsorption of organic molecules to carbonaceous particles enhances their penetration into the respiratory portions of the lungs because these molecules follow the deposition and uptake pathways of the particles and end up in macrophages. Once adsorbed onto particles, however, these molecules become less bioavailable because of high-energy binding and the lesser ability of biologic than of chemical fluids to desorb them. Thus mechanisms of carcinogenesis, which are operative in vitro

with nonadsorbed mutagenic organic compounds, may not be extrapolated to mechanisms in vivo in which these same compounds are adsorbed to particle surfaces.

REFERENCES

- Adamson YR, Bowden DH. 1981. Dose response of the pulmonary macrophagic system to various particulates and its relationship to transepithelial passage of free particles. *Exp Lung Res* 2:165-175.
- Albert RE, Spiegelman JR, Lippmann M, Bennett R. 1968. The characteristics of bronchial clearance in the miniature donkey. *Arch Environ Health* 17:50-58.
- Bailey MR, Fry FA, James AC. 1982. The long-term clearance kinetics of insoluble particles from the human lung. *Ann Occup Hyg* 26:273-290.
- Bellmann B, Muhle H, Heinrich U. 1983. Lung clearance after long time exposure of rats to airborne pollutants. *J Aerosol Sci* 14:194-196.
- Bohning DE, Atkins HL, Cohen SH. 1982. Long-term particle clearance in man: Normal and impaired. *Ann Occup Hyg* 26:259-271.
- Bond JA, Butler MM, Medinsky MA, Muggenburg BA, McClellan RO. 1984. Dog pulmonary macrophage metabolism of free and particle-associated [^{14}C]benzo[*a*]pyrene. *J Toxicol Environ Health* 14:181-189.
- Bond J, Sun JD, Medinsky MA, Jones RK, Yeh HC. 1986. Deposition, metabolism, and excretion of 1-[^{14}C]nitropyrene and 1-[^{14}C]nitropyrene coated on diesel exhaust particles as influenced by exposure concentration. *Toxicol Appl Pharmacol* 85:102-117.
- Bond JA, Wolff RK, Harkema JR, Mauderly JL, Henderson RF, Griffith WC, McClellan RO. 1988. Distribution of DNA adducts in the respiratory tract of rats exposed to diesel exhaust. *Toxicol Appl Pharmacol* 96:336-346.
- Brooks AL, Wolff RK, Royer RE, Clark CR, Sanchez A, McClellan RO. 1981. Deposition and biological availability of diesel particles and their associated mutagenic chemicals. *Environ Int* 5:263-267.
- Chan TL, Lee PS, Hering WE. 1981. Deposition and clearance of inhaled diesel exhaust particles in the respiratory tract of Fischer rats. *J Appl Toxicol* 1:77-82.
- Chan TL, Lee PS, Hering WE. 1984. Pulmonary retention of inhaled diesel particles after prolonged exposures to diesel exhaust. *Fundam Appl Toxicol* 4:624-631.

- Chan TL, Lippmann M. 1980. Experimental measurements and empirical modeling of the regional deposition of inhaled particles in humans. *Am Ind Hyg Assoc J* 41:399.
- Chen LC, Schlesinger RB. 1983. Response of the bronchial mucociliary clearance system in rabbits to inhaled sulfite and sulfuric acid aerosols. *Toxicol Appl Pharmacol* 71:123-131.
- Creasia DA, Poggenburg JK Jr, Nettekheim P. 1976. Elution of benzo(a)pyrene from carbon particles in the respiratory tract of mice. *J Toxicol Environ Health* 1:962-965.
- Creutzenberg O, Bellmann B, Heinrich U, Fuhs R, Koch W, Mule H. 1990. Clearance and retention of inhaled diesel exhaust particles, carbon black, and titanium dioxide in rats at lung overload conditions. *J Aerosol Sci* 21(Suppl):S455-S458.
- Cuddihy RG, Brownstein RG, Raabe OG, Kanapilly GM. 1973. Respiratory tract deposition of inhaled polydisperse aerosols in beagle dogs. *J Aerosol Sci* 4:35-45.
- Dutcher JS, Sun JD, Lopez JA, Wolf I, Wolff RK, McClellan RO. 1984. Generation and characterization of radiolabelled diesel exhaust. *Am Ind Hyg Assoc J* 45:491-498.
- Ebert LB. 1990. Is soot composed predominately of carbon clusters? *Science* 247:1468-1474.
- Ferin J, Feldstein ML. 1978. Pulmonary clearance and hilar lymph node content in rats after particle exposure. *Environ Res* 16:342-352.
- Frey JW, Corn M. 1967. Physical and chemical characteristics of particulates in a diesel exhaust. Presented at the Aerosol Technology Session, American Industrial Hygiene Association Annual Meeting, Chicago, IL.
- Gerde P, Medinsky MA, Bond JA. 1991. Contemporary issues in toxicology: Particle-associated polycyclic aromatic hydrocarbons—A reappraisal of their possible role in pulmonary carcinogenesis. *Toxicol Appl Pharmacol* 108:1-13.
- Gerde P, Scholander P. 1989. An experimental study of the penetration of polycyclic aromatic hydrocarbons through a model of the bronchial lining layer. *Environ Res* 48:287-295.
- Green GM. 1973. Alveolobronchiolar transport mechanisms. *Arch Intern Med* 131:109-114.
- Griffis LC, Wolff RK, Henderson RF, Griffith WC, Mokler BV, McClellan RO. 1983. Clearance of diesel soot particles from rat lung after a subchronic diesel exhaust exposure. *Fundam Appl Toxicol* 3:99-103.
- Henderson RF, Pickrell JA, Jones RK, Sun JD, Benson JM, Mauderly JL, McClellan RO. 1988. Response of rodents to inhaled diluted diesel exhaust: Biochemical and cytological changes in bronchoalveolar lavage fluid and in lung tissue. *Fundam Appl Toxicol* 11:546-567.
- Heyder J, Gebhart J, Rudolf G, Schiller CF, Stahlhofen W. 1986. Deposition of particles in the human respiratory tract in the size range 0.005-15 μm . *J Aerosol Sci* 17:811-825.
- Holma B. 1967. Short-term lung clearance in rabbits exposed to a radioactive bi-disperse (6 and 3 μm) polystyrene aerosol. In: *Inhaled Particles and Vapours, II* (Davies CN, ed.) pp. 189-195. Pergamon, Oxford, England.
- International Agency for Research on Cancer. 1989. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Diesel and Gasoline Engine Exhausts and Some Nitroarenes, Vol. 46. International Agency for Research on Cancer, Lyon, France.
- Jakob GJ, Risby TH, Hamenway DR. 1992. Use of physical chemistry and in vivo exposure to investigate the toxicity of formaldehyde bound to carbonaceous particles in the murine lung. Research Report No. 53. Health Effects Institute, Cambridge, MA.
- King LC, Kohan MJ, Austin AC, Claxton LD, Huising JL. 1981. Evaluation of the release of mutagens from diesel particles in the presence of physiological fluids. *Environ Mutagen* 3:109-121.
- King LC, Loud K, Tejada SB, Kohan MJ, Lewtas J. 1983. Evaluation of the release of mutagens and 1-nitropyrene from diesel particles in the presence of lung macrophages in culture. *Environ Mutagen* 5:577-586.
- Kleinman MT, Mautz WJ. 1991. The effects of exercise on dose and dose distribution of inhaled automotive pollutants. Research Report No. 45. Health Effects Institute, Cambridge, MA.
- Laube BL, Swift DL, Wagner HN Jr, Norman PS, Adams KL III. 1986. The effect of bronchial obstruction on central airway deposition of a saline aerosol in patients with asthma. *Am Rev Respir Dis* 133:740-743.
- Lee PS, Chan TL, Hering WE. 1983. Long-term clearance of inhaled diesel exhaust particles in rodents. *J Toxicol Environ Health* 12:801-813.
- Lee PS, Gorski RA, Hering WE, Chan TL. 1987. Lung clearance of inhaled particles after exposure to carbon black generated from a resuspension system. *Environ Res* 43:364-373.

- Lehnert BE, Sebring RJ, Oberdörster G. 1994. Pulmonary macrophages: Phenomena associated with "particle overload" condition. In: *Toxic and Carcinogenic Effects of Solid Particles in the Respiratory Tract* (Mohr U, Dungworth DL, Mauderly JL, Oberdörster G, eds.) pp. 159-176. International Life Sciences Institute Press, Washington, DC.
- Leikauf GD. 1978. Particle deposition and clearance in the rabbit respiratory tract. M.A. thesis, New York University.
- Lippmann M. 1977. Regional deposition of particles in the human respiratory tract. In: *Handbook of Physiology, Section IX, Reactions to Environmental Agents* (Lee DHK, Galk HL, Murphy SD, eds.) pp. 213-232. American Physiological Society, Bethesda, MD.
- Lippmann M, Schlesinger RB. 1984. Interspecies comparisons of particle deposition and mucociliary clearance in tracheobronchial airways. *J Toxicol Environ Health* 13:441-469.
- Mauderly JL, Bice DE, Carpenter RL, Gillett NA, Henderson RF, Pickrell JA, Wolff RK. 1987. Effects of inhaled nitrogen dioxide and diesel exhaust on developing lung. Research Report No. 8. Health Effects Institute, Cambridge, MA.
- Mauderly JL, Bice DE, Cheng YS, Gillett NA, Henderson RF, Pickrell JA, Wolff RK. 1989. Influence of experimental pulmonary emphysema on toxicological effects from inhaled nitrogen dioxide and diesel exhaust. Research Report No. 30. Health Effects Institute, Cambridge, MA.
- Mauderly JL, Jones RK, Henderson RF, Wolff RK, Pickrell JA, McClellan RO, Gillett NA. 1988. Relationship of lung structural and functional changes to accumulation of diesel exhaust particles. In: *Inhaled Particles VI* (Dodgson J, McCullum RI, Bailey MR, Fisher DR, eds.) pp. 659-669. Pergamon, Oxford, England.
- Mauderly JL, Jones RK, McClellan RO, Henderson RF, Griffith WC. 1986. Carcinogenicity of diesel exhaust inhaled chronically by rats. In: *Carcinogenic and Mutagenic Effects of Diesel Engine Exhaust* (Ishinishi N, Koizumi A, McClellan RO, Stöber W, eds.) pp. 397-409. Elsevier Science Publishing Co., New York, NY.
- Mauderly JL, McClellan RO, Mokler BV, Redman HC. 1982. Pulmonary responses of Fisher 344 rats and CD-1 mice to exposure to diesel exhaust. *Toxicologist* 2:50.
- Mauderly JL, Snipes MB, Barr EB, Belinsky SA, Bond JA, Brooks AL, Chang I-Y, Cheng YS, Gillett NA, Griffith WC, Henderson RF, Mitchell CE, Nikula KJ, Thomassen DG. 1994. Pulmonary toxicity of inhaled diesel exhaust and carbon black in chronically exposed rats. Research Report No. 68. Health Effects Institute, Cambridge, MA.
- McClellan RO. 1986. Opening remarks: Toxicological effects of emission from diesel engines. In: *Carcinogenic and Mutagenic Effects of Diesel Engine Exhaust* (Ishinishi N, Koizumi A, McClellan RO, Stöber W, eds.) pp. 3-8. Elsevier Science Publishing Co., New York, NY.
- McClellan RO. 1990. Particle overload in the lung: Approaches to improving our knowledge. *J Aerosol Med* 3(Suppl.):197-207.
- McClellan RO, Bice DE, Cuddihy RC, Gillett NA, Henderson RF, Jones RK, Mauderly JL, Pickrell JA, Shami SG, Wolff RK. 1986. Health effects of diesel exhaust. In: *Aerosols: Research, Risk, and Control Strategies* (Lee SD, Schneider T, Grant LD, Verkerk PJ, eds.) pp. 597-615. Lewis Publishers, Chelsea, MI.
- McClellan RO, Brooks AL, Cuddihy RC, Jones RK, Mauderly JL, Wolff RK. 1982. Inhalation toxicology of diesel exhaust particles. In: *Toxicological Effects of Emissions from Diesel Engines* (Lewtas J, ed.). Elsevier Science Publishing Co., New York, NY.
- Morrow PE. 1988. Possible mechanisms to explain dust overloading of the lungs. *Fundam Appl Toxicol* 10:369-384.
- Morrow PE, Muhle H, Mermelstein R. 1981. Chronic inhalation study findings as a basis for proposing a new occupational dust exposure limit. *J Am Coll Toxicol* 10:279-290.
- Oberdörster G. 1988. Lung clearance of inhaled insoluble and soluble particles. *J Aerosol Med* 1:289-330.
- Oberdörster G. 1994. Extrapolation of results from animal inhalation studies with particles to humans. In: *Toxic and Carcinogenic Effects of Solid Particles in the Respiratory Tract* (Mohr U, Dungworth DL, Mauderly JL, Oberdörster G, eds.) pp. 335-353. International Life Sciences Institute Press, Washington, DC.
- Oberdörster G, Ferin J, Morrow PE. 1992. Volumetric loading of alveolar macrophages (AM): Possible basis for diminished AM-mediated particle clearance. *Exp Lung Res* 18:87-104.
- Oberdörster G, Green FHY, Freedman AP. 1984. Clearance of $^{59}\text{Fe}_2\text{O}_3$ particles from the lungs of rats during exposure to coal mine dust and diesel exhaust. *J Aerosol Sci* 15:235-237.

- Oberdörster G, Pepelko W. 1992. Research needs for risk assessment of inhaled particulate matter: Report of a workshop sponsored by the Office of Health and Environmental Assessment, U.S. Environmental Protection Agency, McLean, VA. March 10-11, 1992.
- Pepelko WE. 1987. Feasibility of dose adjustment based on differences in long-term clearance rates of inhaled particulate matter in humans and laboratory animals. *Regul Toxicol Pharmacol* 7:236-252.
- Raabe OG, Yeh H-C, Newton GJ, Phalen RF, Velasquez DJ. 1977. Deposition of inhalable monodisperse aerosols in small rodents. In: *Inhaled Particles IV* (Walton WH, ed.) pp. 3-21. Pergamon, Oxford, England.
- Schlesinger RB. 1975. The intrabronchial pattern of particle deposition. Ph.D. dissertation, New York University.
- Schlesinger RB. 1980. Biological disposition of airborne particles: Basic principles and application to vehicular emissions. In: *Air Pollution, the Automobile, and Public Health* (Watson AY, Bates RR, Kennedy D, eds.) pp. 239-298. National Academy Press, Washington DC.
- Schlesinger RB, Halpern M, Albert RE, Lippmann M. 1979. Effect of chronic inhalation of sulfuric acid mist upon mucociliary clearance from the lungs of donkeys. *J Environ Pathol Toxicol* 2:1351-1367.
- Schlesinger RB, Lippmann M. 1978. Selective particle deposition and bronchogenic carcinoma. *Environ Res* 15:424-431.
- Slak J-S, Chan TL, Lee PS. 1980. Diesel particulate extracts in bacterial test systems. In: *Health Effects of Diesel Engine Emissions* (Pepelko WE, Danner RM, Clarke AN, eds.) pp. 245-262. U.S. Environmental Protection Agency, Cincinnati, OH.
- Snipes MB. 1989. Long-term retention and clearance of particles inhaled by mammalian species. *Crit Rev Toxicol* 20:175-202.
- Snipes MB, Buecker BB, McClellan RO. 1983. Retention of monodisperse or polydisperse aluminosilicate particles inhaled by dogs, rats, and mice. *Toxicol Appl Pharmacol* 68:343-363.
- Soderholm SC. 1982. Compartmental analysis of diesel particle kinetics in the respiratory system of exposed animals. In: *Diesel Emission Symposium Proceedings*. EPA/600/19-82/014. U.S. Environmental Protection Agency, Research Triangle Park, NC. National Technical Information Service, Springfield, VA.
- Sorokin SP, Brain JD. 1974. Pathways of clearance in mouse lungs exposed to iron oxide particles. *Anat Rec* 181:581-626.
- Stahlhofen W, Gehhart J, Heyder J. 1980. Experimental determination of the regional deposition of aerosol particles in the human respiratory tract. *Am Ind Hyg Assoc J* 41:385.
- Stöber W, Morrow PE, Hoover MD. 1989. Compartmental modeling of the long-term retention of insoluble particles deposited in the alveolar region of the lung. *Fundam Appl Toxicol* 13:823-842.
- Stöber W, Morrow PE, Morawietz G. 1990. Alveolar retention and clearance of insoluble particles in rats simulated by a new physiology-oriented compartmental kinetics model. *Fundam Appl Toxicol* 15:329-349.
- Strom KA. 1984. Response of pulmonary cellular defenses to the inhalation of high concentrations of diesel exhaust. *J Toxicol Environ Health* 13:919-944.
- Strom KA, Garg BD, Johnson JT, D'Arcy JB, Smiler KL. 1990. Inhaled particle retention in rats receiving low exposures of diesel exhaust. *J Toxicol Environ Health* 29:377-398.
- Strom KA, Johnson JT, Chan TL. 1989. Retention and clearance of inhaled submicron carbon black particles. *J Toxicol Environ Health* 26:183-202.
- Sun JD, McClellan RO. 1984. Respiratory tract clearance of ¹⁴C-labeled diesel exhaust compounds associated with diesel particles or as a particle-free extract. *Fundam Appl Toxicol* 4:388-393.
- Sun JD, Wolff RK, Aberman HM, McClellan RO. 1983. Inhalation of 1-nitropyrene associated with ultrafine insoluble particles or as a pure aerosol: A comparison of deposition and biological fate. *Toxicol Appl Pharmacol* 69:185-198.
- Sun JD, Wolff RK, Kanapilly GM, McClellan RO. 1984. Lung retention and metabolic fate of inhaled benzo[a]pyrene associated with diesel exhaust particle. *Toxicol Appl Pharmacol* 73:48-59.
- Sun JD, Wolff RK, Maio SM, Barr EB. 1989. Influence of adsorption to carbon black particles on the retention and metabolic activation of benzo[a]pyrene in rat lungs following inhalation exposure or intratracheal instillation. *Inhalation Toxicol* 1:1-19.
- Valberg PA, Brian JD, Sneddon SL, LeMott SR. 1982. Breathing patterns influence aerosol deposition sites in excised dog lungs. *J Appl Physiol* 53:824-837.

Vostal JJ. 1983. Bioavailability and biotransformation of the mutagenic component of particulate emissions present in motor exhaust samples. *Environ Health Perspect* 47:269-281.

Vostal JJ. 1986. Factors limiting the evidence for chemical carcinogenicity of diesel emissions in long-term inhalation experiments. In: *Carcinogenic and Mutagenic Effects of Diesel Engine Exhaust* (Ishinishi N, Koizumi A, McClellan RO, Stöber W, eds.) pp. 381-396. Elsevier Science Publishing Co., New York, NY.

Wolff RK, Henderson RF, Snipes MB, Griffith WC, Mauderly JL, Cuddihy RG, McClellan RO. 1987. Alterations in particle accumulation and clearance in lungs of rats chronically exposed to diesel exhaust. *Fundam Appl Toxicol* 9:154-166.

Wolff RK, Sun JD, Barr EB, Rothenberg SJ, Yeh HC. 1989. Lung retention and binding of [¹⁴C]-1-nitropyrene when inhaled by F344 rats as a pure aerosol or adsorbed to carbon black particles. *J Toxicol Environ Health* 26:309-325.

Wolff RK, Sun JD, Wolf I, Lopez J, Cheng YS, McClellan RO. 1981. Deposition and retention of ⁶⁷Ga-labeled diesel particles. *Inhalation Toxicology Research Institute Annual Report, 1980-1981*, National Technical Information Service, Springfield, VA.

Yeh H-C, Schum GM. 1980. Models of human lung airways and their applications to inhaled particle deposition. *Bull Math Biol* 42:461-480.

Yu CP, Morrow PE, Chan TL, Strom KA, Yoon KJ. 1988. A nonlinear model of alveolar clearance of insoluble particles from the lung. *Inhalation Toxicol* 1:97-107.

Yu CP, Xu GB. 1986. Predictive models for deposition of diesel exhaust particulates in human and rat lungs. *Aero Sci Technol* 5:337-347.

Yu CP, Xu GB. 1987a. Predicted deposition of diesel particles in young humans. *J Aerosol Sci* 18:419-429.

Yu CP, Xu GB. 1987b. Predictive models for deposition of inhaled diesel exhaust particles in humans and laboratory species. *Research Report No. 10*, Health Effects Institute, Cambridge, MA.

Yu CP, Yoon KJ. 1991. Retention modeling of diesel exhaust particles in rats and humans. *Research Report No. 40*, Health Effects Institute, Cambridge, MA.

ABBREVIATIONS

BaP	benzo(a)pyrene
¹⁴ C	carbon 14
¹³⁴ Cs	cesium-134
¹³⁴ Cs-FAP	¹³⁴ Cs-fused aluminosilicate particles
⁵⁶ Fe ₂ O ₃	iron oxide
⁶⁷ Ga ₂ O ₃	gallium oxide
PAH	polycyclic aromatic hydrocarbon
SD	standard deviation
SE	standard error

From: Barsic Nicholas J 319-292-8152 fax 319-292-8457
Date: Friday, February 4, 1998
To: Glenn Keller, Bill Bunn 312-245-1085 312-836-2221
Subject: Smoking comments in the literature

Several published reports have commented on the manner in which smoking has been addressed by various epidemiologic studies. The essence of these comments is that the epidemiologic impact of cigarette smoking is so much stronger than, for example, diesel particulate matter, that the independent health impact of diesel may have been overestimated in many cases. Stated another way, the relative risk due to smoking, which is 5 to 10 times greater than that presently estimated for diesel exhaust, may have resulted in an upward bias for the relative risk of diesel exhaust particles. Thus, future investigations require more careful control for smoking and other occupational substances than has been provided in past studies in order to reach definitive conclusions on the true health impact of diesel exhaust particles. The following quotes from peer-reviewed journal articles support this suggestion.

McClellan, R.O., Cuddihy, R.G., Griffith, W.C., and Mauderly, J.L., "1. Integrating Diverse Data Sets to Assess the Risks of Airborne Pollutants," In: Assessment of Inhalation Hazards, eds: D.V. Bates, D.L. Dungworth, P.N. Lee, R.O. McClellan, F.J.C. Roe, ILSI Monographs, 1989, p. 10.

"In evaluating the Garshick et al. (1987, 1988) studies, several considerations are worthy of note. As is frequently the question in lung cancer studies, the extent to which the cigarette smoking history of the subjects has been taken into account is of paramount importance. The extent to which misclassification by smoking history can influence the results is clear from a comparison in Table 1.2 (same as Garshick, 1987, Table 4) of the odds ratios for cigarette smoking with those for 20 years of diesel exhaust exposure. The added risk of less than 50 pack-years of smoking in the under 64 year age group was more than 5 times that of 20 years of diesel exhaust exposure (2.29 versus 0.41), and for the over 50 pack-year group, more than 11 times that of 20 years of diesel exhaust exposure (4.68 versus 0.41). This, coupled with the potential for survivors tending to underestimate smoking in the face of a potential occupational factor, diesel exhaust exposure, leaves open the issue of whether the ascertainment of smoking history was adequate."

Mauderly, J.L., "Diesel Exhaust" In: Environmental Toxicants – Human Exposures and Their Health Effects, Chapter 5 (M. Lippmann, ed.), 1992

"Yet another difficulty results from the ubiquitous distribution of diesel exhaust and the overlapping of its composition with other ubiquitous pollutant mixtures such as gasoline engine exhaust and other fossil fuel combustion effluents. All individuals are exposed: no clearly exposed and unexposed populations are available for study. For the purposes of this review, the terms "exposed" and "unexposed" are used in reference to study groups contrasted by authors of the reports, although the precise definition varies from study to study. Finally, information on tobacco smoking was only obtained in approximately one-half of the studies. Because the relative risk for lung cancer among smokers is much greater than that indicated for diesel exhaust exposures, small imbalances in smoking among "diesel-exhaust exposed" and "unexposed" groups could have markedly affected the apparent relationship between diesel exhaust exposure and lung cancer." P. 126

"The importance of misclassification and adjustment for smoking is illustrated by the magnitude of smoking-related risks reported in the above studies. As examples, the relative risk for lung cancer ranged from 5.7 for railroad workers with more than 50 pack-years of smoking history in the Garshick et al. (1987) study to 21.0 for smokers of more than 31 cigarettes/day in the Hall and Wynder (1984) study. Small misclassifications of subjects in the adjustments for smoking could thus skew the apparent diesel-exhaust-related risks for lung cancer." p. 135

Schenker, M.B., "27. Epidemiologic Studies of Populations Exposed to Motor Vehicle Exhausts and Polycyclic Aromatic Hydrocarbons," In: Assessment of Inhalation Hazards, eds: D.V. Bates, D.L. Dungworth, P.N. Lee, R.O. McClellan, F.J.C. Roe, ILSI Monographs, 1989, p. 296.

"The very small estimated risk from environmental pollution also increases the difficulty of excluding the distinct possibility that observed effects are occurring as a result of confounding by cigarette smoking or even occupational exposures (Hammond and Garfinkel, 1980). Differences in smoking habits can exist for different geographic areas, and not be reflected in smoking prevalence. For example, the age at which individuals begin smoking, duration of smoking, and manner of smoking may partially explain the urban-rural difference in lung cancer rates (Doll, 1987; Hammond and Garfinkel, 1980). Failure to control for such differences may result in failure to observe an effect, or in confounding of results.

Lee, P.N., "4. Problems in Interpreting Epidemiologic Data," In: Assessment of Inhalation Hazards, eds: D.V. Bates, D.L. Dungworth, P.N. Lee, R.O. McClellan, F.J.C. Roe, ILSI Monographs, 1989, p. 55.

"Epidemiology is quite satisfactory for isolating true effects provided the association is a strong one. As the association studied becomes progressively weaker, problems caused by non-reporting, misclassification and confounding become relatively more important. Particularly for weak associations, with relative risks of less than 2, it is of vital importance to consider all the possibilities of bias. It may be impossible to make reliable inferences. As an example of the difficulties in interpretation, the weak association between ETS and lung cancer ..."

p. 57: "... 5% of smokers denying smoking has the result of converting true relative risks of 20 for active smoking and 1 for passive smoking into observed relative risks of 10.5 for active smoking and 1.75 for passive smoking."

p. 58: "In any non-randomized epidemiological study with a relative risk less than 2, great care must be taken before inferring causality. The closer the relative risk is to 1, the more severe the problems of interpretation due to one or more of the various sources of bias... Until more attention is paid to these points, it will remain likely that many reports of statistically significant but weak associations will be false-positives."

Morgan, W.K.C., Reger, R.B., Tucker, D.M., "Health Effects of Diesel Emissions," *Am. Occup Hyg.*, Vol. 4, No. 6, pp. 643-658, 1997.

p. 648, "Hall and Wynder (1984) conducted a case-control study of lung cancer in subjects exposed to diesel exhaust. They observed a strong association of lung cancer with cigarette smoking and a two-fold increase in lung cancer for those exposed to diesel exhaust. When allowance was made for smoking, the excess lung cancer first attributed to diesel exposure disappeared. "

p. 650: "Confounding by cigarette smoking can easily explain an RR of 1.5 – 2 as shown in previous studies."

p. 652: "Boffetta et al. (1989, 1990) later reported on a lung cancer case-control study of workers with probable exposure to diesel exhaust emissions." ... "While the crude odds ratio for those probably exposed to diesel exhaust was 1.31, this decreased to less than unity after accounting for the effects of cigarette smoking."

**Comments Of The Engine Manufacturers Association Regarding
The ARB/OEHHA Draft Report**

**"Proposed Identification Of Diesel Exhaust As A Toxic
Air Contaminant, May, 1997"**

Dated: August 22, 1997

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I. Introduction

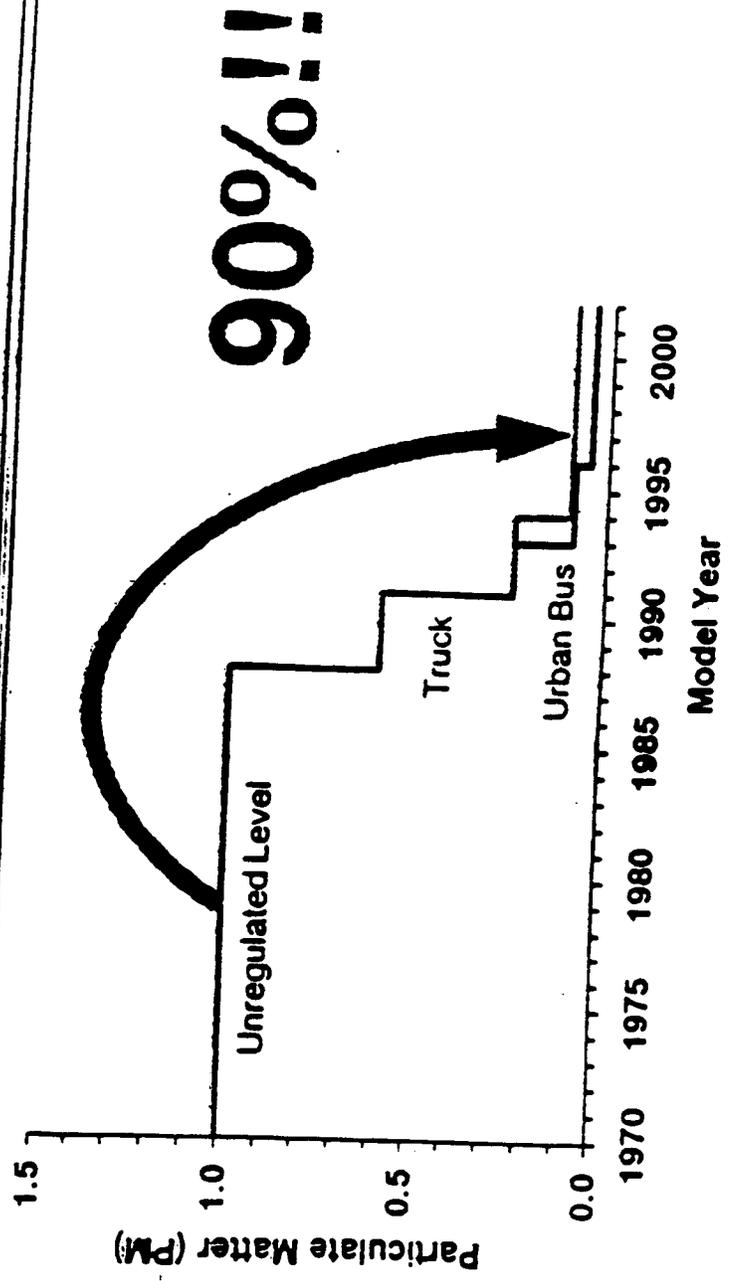
The Engine Manufacturers Association (EMA) is the trade association that represents worldwide manufacturers of engines for all applications other than passenger cars and aircraft. Included among the many products manufactured by the more than 35 major corporations that comprise EMA are a full array of diesel engines. Through the cooperative efforts of EMA and its members, working in conjunction with federal and state regulatory agencies, including ARB, dramatic engine design improvements and emissions reductions have been obtained. A particularly relevant example of these advancements (as reflected on the chart on p. 1A) is that emissions of diesel particulate matter have been reduced by 90% over the past ten years.

The ARB/OEHHA report at issue -- specifically, "Part B" of the "Proposed Identification of Diesel Exhaust as a Toxic Air Contaminant" (hereinafter, the "Draft Report") -- is of vital importance to EMA and its members. In fact, the potential public policy effects from the Draft Report are such that the diesel engine industry will take all necessary measures to ensure that any final report actually utilizes and reflects "the best available scientific evidence" and "sound scientific knowledge," as mandated by law.

The current Draft Report (OEHHA's second effort) falls well short of the mark. More specifically, in its second Draft Report, OEHHA has once again elected to rely primarily on Dr. Mauderly's study of rats and Dr. Garshick's study of railroad workers to construct a quantitative risk assessment. In so doing, OEHHA has ignored those researchers' otherwise clear cautions, and has taken positions deemed unjustified by every other national and international body that has considered this issue within the past several years. OEHHA has also ignored the current data indicating that a non-linear dose-response function should be examined and utilized. Finally, OEHHA is pursuing a listing for "diesel exhaust," as opposed to any specific constituent(s) thereof, which as a practical matter (even overlooking the lack of scientific justification for such a listing) makes no sense whatsoever.

Consequently, the Draft Report must be revised substantially to reflect the significant scientific uncertainties that preclude the conclusions that OEHHA has attempted to justify. The principal uncertainties undermining the Draft Report are detailed in the attached reports from EMA's consulting experts -- Dr. Peter Valberg and Dr. Tony Cox. These expert reports, copies of which are appended hereto as Exhibits A and B, along with the other comments concerning the Draft Report that OEHHA has received from the leading researchers in this area (e.g. Drs. Mauderly, McClellan and Moolgavkar) confirm beyond any legitimate dispute that the overall findings and conclusions of the Draft Report are unsubstantiated, and by no means reflect the best available science. In fact, OEHHA has manipulated, misrepresented or contradicted the findings of many of the health studies cited in the Report, as indicated expressly by the principal authors of those studies at the July 1 workshop.

PM Reductions to Date



In sum, OEHHA should cease misrepresenting the current scientific understanding of the carcinogenic potential of diesel engine exhaust, and should accept the fact that the inherent limitations of the underlying data cannot justify the quantitative risk assessment that OEHHA has constructed. Since OEHHA has not done that, the Draft Report remains fundamentally flawed, as detailed below.

II. The Draft OEHHA Report Is Scientifically Inadequate

The ultimate conclusion of the Draft OEHHA Report is that ambient day-to-day exposures to "diesel exhaust" at concentrations of 2.2 ug/m³ will cause up to approximately 2,143 lung cancer deaths per year in California [150,000 deaths ÷ 70 years]. "Sound scientific knowledge" -- the mandatory benchmark of the TAC review process -- does not support this purported conclusion. Indeed, if OEHHA were correct, it would mean that diesel exhaust, presumably diesel exhaust particulate matter, would kill approximately 16,400 people each year in the U.S. [2,143 x (260MM ÷ 34MM)]. But that is more than the total of 15,000 premature deaths that U.S. EPA has attributed to all particulate matter (not just diesel exhaust particulate) in this country. OEHHA's conclusions therefore belie common sense as well as EPA's much-publicized studies concerning the health effects allegedly associated with particulate matter.

OEHHA's conclusions, then, clearly do not reflect the best available scientific evidence relating to this issue. In fact, as the following discussion demonstrates, many of the premises that OEHHA proffers as support for its conclusions are not scientifically defensible. This renders the Draft Report, as a whole, scientifically inadequate.

a. The Animal/Rat Studies

Over the past five years, the conclusions to be drawn from the earlier inhalation studies of rats have changed dramatically. What was known in the 1980's was that lung tumors could be induced in rats if you exposed them for nearly their entire lifetimes to exceedingly high levels of concentrated diesel exhaust (2,000-10,000 ug/m³ v. ambient concentrations of 2.2 ug/m³). What has been learned since then is that:

- Whole diesel exhaust is not genotoxic in laboratory tests.
- To be biologically effective, the organic fraction of diesel exhaust must be extracted with strong solvents and then concentrated.
- Even if bioavailable, the total quantity of the organic fraction of diesel particulate is in all likelihood too small to have any effect.
- The organic fraction of diesel exhaust is not necessary for tumor induction in rats.

Consequently, the tumor response in rats is now believed to be initiated by a physiological response to particulate matter. But (as depicted on the chart on p. 3A) the response can be duplicated for many types of inert particles -- not just diesel particulate -- and requires lung "overload." Thus, the growing scientific consensus is that the observed tumor response is a species-specific response (significant lung inflammation and cell proliferation) unique to the rat. The rat, then, has been found to be an "outlier." In addition, the data demonstrate that there is a threshold below which no response is triggered.

Faced with these findings, the conclusions of the leading research organizations and experts (in addition to those set forth in the appended expert reports) are most instructive:

A. Health Effects Institute Special Report: Diesel Exhaust: A Critical Analysis of Emissions, Exposure, and Health Effects (HEI April, 1995) (hereinafter, "HEI Diesel Report")

- "The lung tumors observed in rats exposed to high concentrations of diesel emissions may be due to a species-specific response to inhaled particulate matter rather than to a carcinogenic mechanism that also occurs in humans." (p.7)
- "[T]he limited data for coal miners suggest that even when particle clearance mechanisms are overwhelmed and the lungs contain heavy particle burdens, cancer does not necessarily develop." (p.50)
- "Most of the U.S. population is exposed to relatively low, long-term average atmospheric concentrations of diesel particulate matter (1 to 10 ug/m³), and for this population the relevance of the rat bioassay data to estimate human lung cancer risk is questionable." (p.50)

B. Correspondence from CASAC Chairman, George Wolff, to Carol M. Browner, Administrator US EPA, dated August 3, 1995

"The cancer-causing mechanism in the rat may be unique to the rat and does not appear to occur in other species, including humans. The mechanism in rats is apparently related to particulate overload followed by a sequence of events beginning with inflammation and ending in tumorigenesis. These events are conditional upon particle overload which also occurs in rats exposed to high concentrations of inert dust as well. Consequently, it appears that these studies are not relevant for human risk assessments."

Chronic Inhalation of Inert Particles and Lung Tumors

<i>Particle Type</i>	<i>Rat</i>	<i>Mice</i>	<i>Hamster</i>	<i>Human</i>
Carbon black	+	-	?	-
Coal dust	+	?	?	-
Diesel exhaust	+	- *	-	(- -)
Iron oxide	?	?	?	-
Talc (non-asb.)	+	-	?	-
Titanium Dioxide	+	-	?	-

* EPA erroneously attributes significant lung tumors to mice, in response to inhaled particle exposure

C. Correspondence from Joe L. Mauderly to US EPA Science Advisory Board, dated May 8, 1995

"The animal carcinogenicity data available for exposure-response modeling come from only one species, the rat, with no comparable response in two other species [mice and hamsters]. Moreover, the weight of evidence (that is growing monthly) strongly suggests that the rat is an outlier in its typical neoplastic response to chronic lung irritation. We have no strong evidence that human lungs behave similarly, and quite suggestive evidence that they do not."

"Tumors occur in rats only under conditions which are not expected to occur in any substantial number of humans, and certainly not as a result of environmental exposure."

"Current thinking is that the rat neoplastic response should not be used for estimating lung cancer risks from exposures two orders of magnitude, or greater, below those of the rats."

That OEHHA would ignore these concerns, especially those of Dr. Mauderly, raises very troubling questions, and provides clear evidence that OEHHA's report does not reflect sound scientific knowledge or the best available evidence. If the rat is not even predictive of other rodents, how can OEHHA be so convinced that the rat is predictive -- quantifiably predictive -- of human responses?

b. The Epidemiologic Studies

The data from the relevant epidemiologic studies are no better. The results of the epidemiologic studies are generally consistent in showing a "weak association" (HEI Diesel Report, p. 6) -- not causation -- between exposure to diesel exhaust in occupational settings and lung cancer. But the increase in relative risk (1.2 to 1.5) was small (see summary chart on p. 4A) and many of the measurements involved were imprecise. As a result, many of the studies are not statistically significant.

In addition, and as detailed in the appended expert reports, many of the studies that OEHHA relies on did not control adequately for confounding factors such as smoking, environmental tobacco smoke, nondiesel particulate matter, asbestos exposure, socioeconomic factors, diet, or exposures to other air pollutants. Even more significantly, the key epidemiologic studies of Garshick, et al. lack any actual exposure data; we do not know the actual exposure levels involved or how the composition of diesel exhaust then at issue compares to today's exhaust. Thus, as HEI has noted,

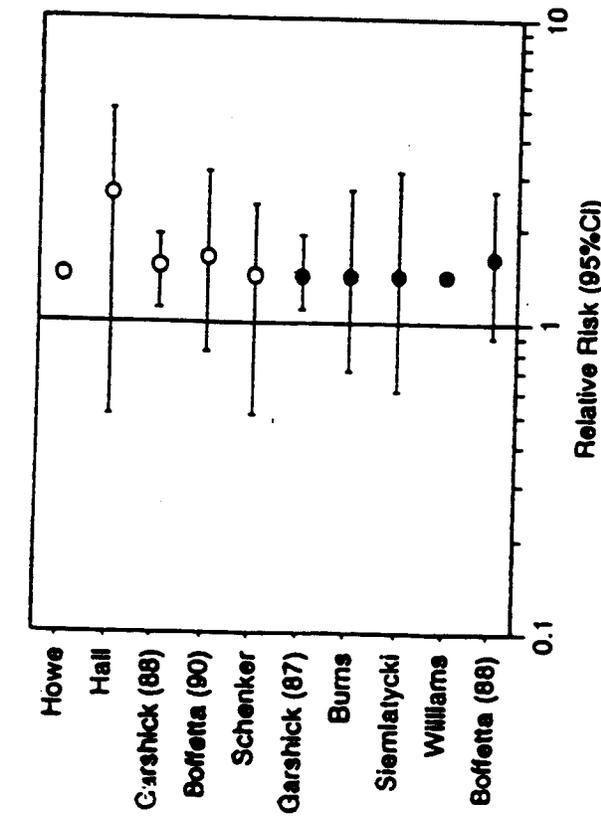


Figure 7. Lung cancer and exposure to diesel exhaust in railroad workers. ● = Relative risk adjusted for cigarette smoking; ○ = relative risk not adjusted for cigarette smoking. For the two studies by Howe and Williams, confidence intervals were not reported and could not be calculated. (Cohen and Higgins, this report.)

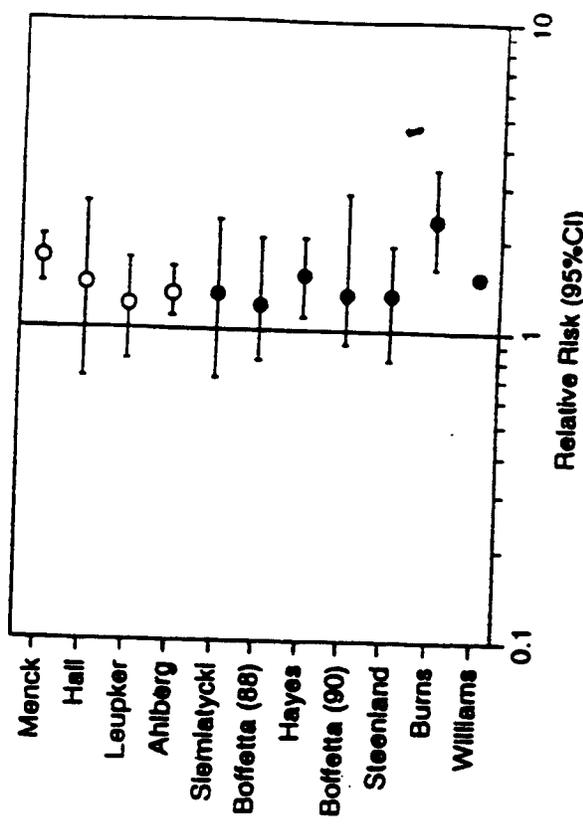


Figure 8. Lung cancer and exposure to diesel exhaust in truck drivers. ● = Relative risk adjusted for cigarette smoking; ○ = Relative risk not adjusted for cigarette smoking. For the study by Williams, confidence intervals were not reported and could not be calculated. For the Steenland study, the data were gathered from union reports of long-haul truck drivers; for the Boffetta (1988) study, the data were self-reported by diesel truck drivers; and for the Siemiatycki study, they were self-reported by heavy-duty truck drivers (personal communication). (Cohen and Higgins, this report.)

"The absence of exposure measurements in the study populations is the main methodologic problem limiting interpretation of the epidemiologic data and its use in quantitative risk assessments." (HEI Diesel Report, p. 28.)

While past epidemiologic studies are fundamentally flawed, it is also important to bear in mind that the composition of diesel fuels and the combustion process that creates exhaust have changed dramatically since the 1960's. These changes (as depicted on the following chart, p. 5A) include:

- 90% reductions in particulate emissions
- HC + CO emissions reduced to 10% of current standards
- 75% reductions in NO_x emissions
- development and use of low sulfur/low aromatics fuels
- development and implementation of advanced diesel engine designs
 - high pressure fuel injection
 - computerized timing
 - turbocharging and charge air cooling
 - improved oil control
 - reshaped combustion chambers

Consequently, what came out of one particular type of diesel engine - locomotives - in the 60's and 70's is simply not the equivalent, either in quantity or composition, of diesel engine emissions today. Given these profound shortcomings, the leading experts continue to caution against relying on the existing epidemiologic data to make any specific or quantitative conclusions:

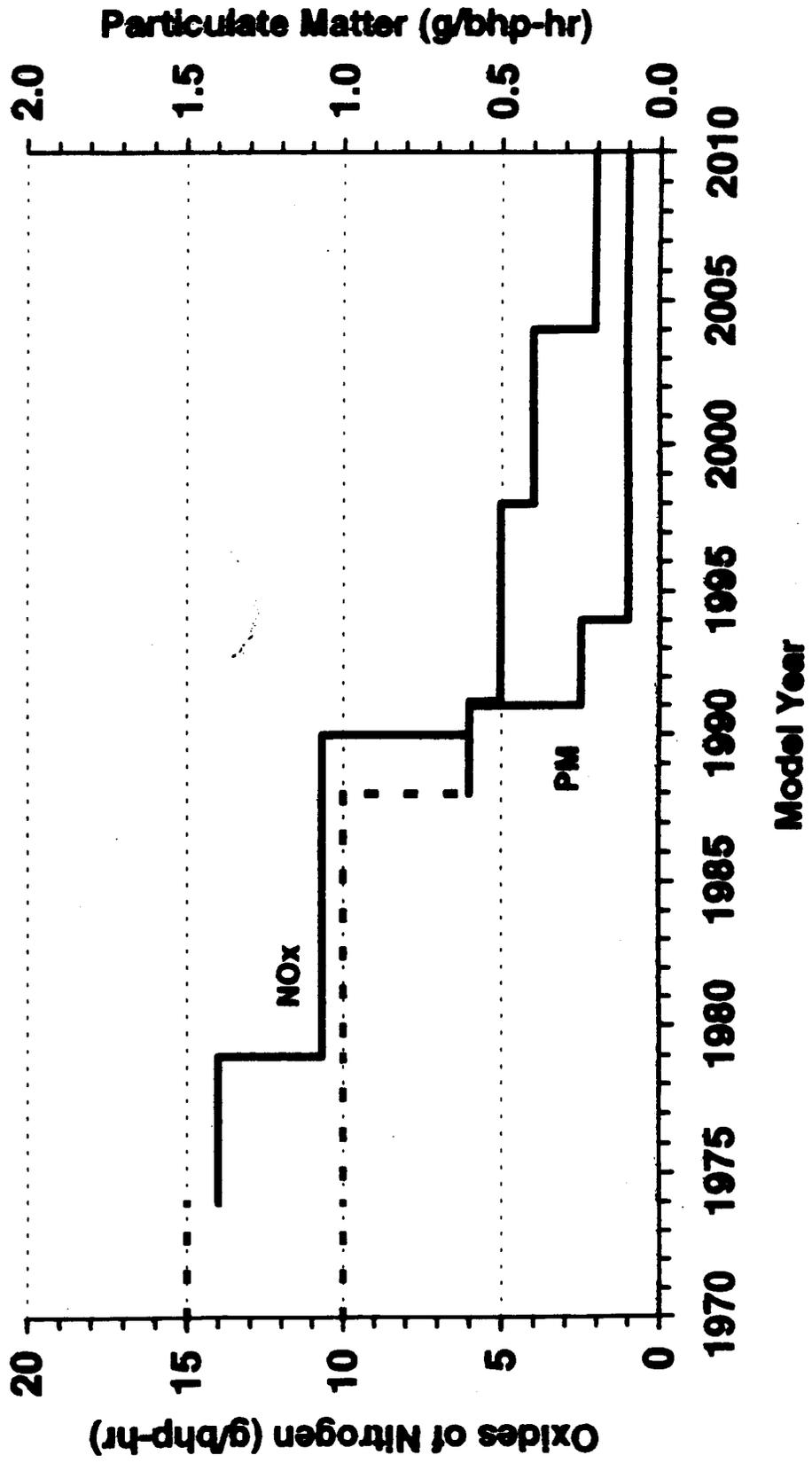
A. HEI Diesel Report

- "The results of most of the studies were not statistically significant." (p.27)
- "[T]he lack of definitive exposure data for the occupationally exposed study populations precludes using the available epidemiologic data to develop quantitative estimates of cancer risk." (p.8)

B. US EPA: Health Assessment Document for Diesel Emissions (September 1994)

- "Human data are preferable for developing risk estimates. However, ... use of the human data are, considered in this case to be inadequate for this purpose. First of all, the relative risk ratios for the human epidemiology studies are generally only slighter greater than one. Small errors in the adjustment for possible

Heavy-Duty Diesel Engine Emission Standards U.S. EPA



confounding factors, especially smoking, could result in a large percentage change in relative risk."

"Finally, an attempt was made to use the Garshick, et al. (1987) railroad worker study to develop a unit risk assessment. However, attempts to relate increasing duration or intensity of exposure to increasing response rates were unsuccessful." (p.12-6)

C. World Health Organization: IPCS, Environmental Health Criteria #171; Diesel Fuel and Exhaust Emissions (1996) (hereinafter, "WHO Diesel Report")

- "[H]istorical measurements of exposure to diesel exhaust are unreliable and exist only for current workers in two industries. A quantitative risk assessment cannot be conducted on the basis of epidemiological data in which job title was used as a surrogate of exposure Consequently, there are no human data suitable for estimating unit risk." (p. 254)

Thus, epidemiologic studies are not recommended for risk assessment by EPA, WHO or HEI. Even, Dr. Eric Garshick -- the researcher upon whom OEHHA principally stakes its claim -- has confirmed to CASAC (see Exhibit C hereto) that his studies do not constitute a sound scientific basis for any quantitative risk assessment.

Correspondence from Eric Garshick to US EPA Science Advisory Board, dated May 30, 1995

"We agree with EPA that a major limitation in the use of this data set and others to conduct a risk assessment is the crudeness of the exposure data and the inability to determine how significantly exposures changed (decreased) over time."

"[I]t is not possible to use the human epidemiologic data that was reanalyzed to assign a unit risk with confidence due to the uncertainty of the exposure data."

More importantly, subsequent analyses of the Garshick data have established that the railroad workers study does not confirm a positive dose-response relationship between increased exposure to diesel exhaust and an increased relative risk for lung cancer. See K. Crump, Statistical Exposure-Response Analysis of a Retrospective Cohort Study of Lung Cancer Mortality in U.S. Railroad Workers Exposed to Diesel Exhaust, Journal of Occupational and Environmental Medicine (submitted 1997). While OEHHA attempts to justify its wholesale rejection of Dr. Crump's analyses on the basis of a supposed cross-tabulation "error" (see Correspondence from Peter D. Venturini to

Glenn Keller, 6/13/97), OEHHA knows full well that the purported "error" has been addressed and that the results of Dr. Crump's analyses still hold true. Thus, as Dr. Crump demonstrated at the July 1 workshop: (i) lung cancer mortality was not significantly elevated among railroad shopworkers in comparison to clerks and signalmen, despite the fact that shopworkers likely had the most intense exposures of any group; (ii) the relative risk of lung cancer tended to decrease with increasing duration of exposure within exposed railroad workers; and (iii) there is no convincing evidence for an effect of diesel exhaust exposure upon lung cancer in the railroad workers cohort.

In response to these otherwise clear limitations (limitations which Dr. Garshick himself has recognized), and as detailed in the Valberg Report, OEHHA has made completely arbitrary adjustments to its reanalyses of the Garshick et al. data in a transparent effort to manufacture a dose-response relationship. This manipulation of the data includes: (i) requantification of historic exposure levels to minimize differences in estimated exposures experienced by shopworkers, on the one hand, and all other exposed workers, on the other hand; (ii) outright exclusion of the shopworkers from the reanalyses, even though they were the workers estimated to have received the largest exposures to diesel exhaust; and (iii) rejection of analyses of the estimated exposures in terms of total lung-deposited amounts of diesel exhaust, apparently because this metric offered the most dramatic illustrations of the absence of any increasing dose-response relationship. OEHHA does not and cannot adequately justify any of these post hoc "adjustments" of the data.

In sum, and as further explained in the attached expert reports, OEHHA's risk assessment pretends that very little is known about the specific causal mechanism of cancer induction in rats, while much is known about diesel exhaust epidemiology. Neither position is accurate. In fact, as evidenced by Dr. Mauderly's comments, a great deal is known about rat lung carcinogenesis in response to over-burdening by diesel exhaust, but this knowledge has not been utilized properly in OEHHA's risk models or estimates. On the other hand, and despite OEHHA's "likely explanations" to the contrary, the epidemiological evidence has failed to establish a causal link between diesel exhaust and development of human lung cancers, and OEHHA's causal interpretation of a relation between diesel exhaust and human lung cancer is unsupported by any statistical tests for causation. In fact, OEHHA did not even run any causality tests. Not surprisingly, then, OEHHA's purported conclusions fly in the face of the principal finding of the Health Effects Institute:

The average levels of diesel exhaust found in most occupational settings, which are below 100 ug/m³, would not likely be a cancer hazard for these workers, nor would ambient levels (1 to 10 ug/m³) present a cancer risk for the general population. . . . [While] one cannot exclude the possibility that [there is] a mechanism involving direct action

between the chemical mutagens in diesel exhaust and DNA . . . the available epidemiologic and animal data are insufficient to support this hypothesis or to be used in quantitative risk assessments. (HEI Diesel Report, pp. 1-2.)

OEHHA's Draft Report is therefore scientifically inadequate, based as it is on studies that even their authors claim are wholly unsuited to quantitative risk assessments. Indeed, the epidemiologic studies in question were not designed for risk-assessment purposes. OEHHA therefore should accept those limitations and acknowledge that it is not possible at this time to quantify a hypothetical risk associated with exposure to diesel exhaust.

c. Non-Linear Dose-Response

The Valberg and Cox Reports amply describe the scientific inadequacies in OEHHA's efforts to justify a linear dose-response relationship between exposure to diesel exhaust and lung cancer. Briefly, since OEHHA is attempting to estimate risks purportedly associated with diesel exhaust exposures much lower than those at issue in either the occupational epidemiologic studies or in the rat bioassay studies, OEHHA must establish a linear relationship to extrapolate down to low ambient doses (i.e. 2.2 ug/m³ v. 2000 ug/m³). But OEHHA cannot support its assertion of a linear relationship, which is typically associated with genotoxic carcinogens.

First, OEHHA cannot establish that the absorbed hydrocarbons (approximately 0.0007%, by weight, of "diesel exhaust"; see WHO Diesel Report, p. 101) are bioavailable or bioactive. Indeed, if human lungs are not under "overload" conditions as a result of diesel exhaust exposures (as OEHHA suggests), and macrophages are not impaired in their ability to take and remove particles, and organic material is not released from the particles by lung surface fluids, then it is difficult to imagine how lung epithelial cells are at risk of exposure to mutagenic organic compounds. Second, experimental data demonstrate a threshold for responses that are mechanistically related to particle-induced tumorigenesis in the rat model. Even Dr. Garshick's analysis suggests that virtually all of the elevated lung cancer risk is associated with occupational exposures exceeding 20 years. And, as noted in the Cox Report, OEHHA's own analysis of the Garshick et al. data indicates that a threshold model is much more plausible than a linear low-dose model. More specifically, Figure 7-3 of the Draft Report shows that relative risks do not increase for the three lowest cumulative exposures, but increase dramatically for the fourth. This data pattern is fully consistent with and supportive of a threshold model. Finally, a mechanism of action for the proposed carcinogenicity of diesel exhaust in humans has not been identified. In rats, as noted above, it appears that the diesel exhaust-induced tumorigenesis is mediated by non-genotoxic mechanisms that exhibit a threshold.

The evidence for genotoxic mechanisms for diesel exhaust is thus entirely speculative and cannot be used to justify a linear dose-response model. This is more than a little significant inasmuch as non-linearity of the dose-response relationship would negate OEHHA's attempts to construct a quantitative risk estimate for low exposures resulting from ambient air.

d. Listing "Diesel Exhaust" Is Nonsensical

In addition to being flawed in its details, the Draft Report is fundamentally unsound in its general objective. The Draft Report seeks a TAC listing for "diesel exhaust," not any particular component of diesel exhaust. But diesel exhaust, by weight, is 75.2% nitrogen, 15.0% oxygen, 7.1% carbon dioxide, and 2.6% water vapor. (See WHO Diesel Report, p. 101.) Thus, it is beyond dispute that 99.9% of "diesel exhaust" is not toxic. A listing for "diesel exhaust" as a whole therefore makes no sense.

Moreover, it remains the case that for as long as there are diesel engines in operation, there will be "diesel exhaust." Even if diesel technology were to advance (which it may) to the point where diesel engine emissions consist solely of nitrogen, oxygen, carbon dioxide and water vapor, those entirely non-toxic emissions would still constitute "diesel exhaust," and so would still be a TAC under the rubric espoused by ARB/OEHHA in the Draft Report. The proposal to list "diesel exhaust" is therefore nonsensical for this reason as well.

Finally, how are regulators or engine manufacturers supposed to respond to a TAC listing for "diesel exhaust?" Such a listing is simply far too broad. The constituents of "diesel exhaust" vary depending upon the engine, the fuel type and the operating conditions at issue. Consequently, "diesel exhaust" is in many respects a continuously evolving and complex mixture of substances, many of which (e.g. particulate matter) are already subject to stringent and effective emission control programs. Consequently, any effective regulatory program must be -- and is -- based upon the identification of one or more specific constituents of "diesel exhaust," not the whole mixture. ARB itself has recognized this necessary regulatory strategy through its negotiation of the Statement of Principles (SOP) that will govern the control of emissions from diesel engines through the year 2004 and beyond. In this case, then, if no specific constituent of diesel exhaust is identified as the supposed toxic agent, what emission constituents should manufacturers and regulators endeavor to reduce beyond the SOP standards? Or is the object of the pending TAC proposal simply the elimination of diesel engines altogether? If not, then the Draft Report must be revised to list the supposed agent that is allegedly responsible for the health effects that OEHHA has hypothesized. In the absence of such a specific listing, OEHHA's proposal will be fundamentally unsound, contrary to existing emission control strategies and, in effect, nonsensical.

For all of the foregoing reasons, and as further explicated in the attached expert reports, the Draft Report is scientifically inadequate. OEHHA therefore should heed the cautions of the leading researchers and concede that, at this juncture, the many significant scientific uncertainties preclude the development of any valid quantitative risk assessment.

III. The Draft OEHHA Report Is Inaccurate If Not Misleading

In addition to being scientifically inadequate, the Draft OEHHA Report is inaccurate if not affirmatively misleading. EMA will present just a sampling of OEHHA's misrepresentations of the relevant data.

Sample #1 -- At pages ES-13 and 1-5 of its report, OEHHA claims that "HEI found that the epidemiological data are consistent in showing associations between exposures to diesel exhaust and lung cancer."

What OEHHA conveniently fails to note, however, is that HEI actually concluded that "the lack of definitive exposure data for the occupationally exposed study populations precludes using the available epidemiologic data to develop quantitative estimates of cancer risk." (HEI Diesel Report, p. 8.) Misrepresenting HEI's conclusions underscores the lack of sound scientific reasoning in the Report.

Sample #2 -- At page 1-7 of its report, OEHHA discusses risk assessments based on occupational studies and claims that "U.S. EPA cited these same . . . values as being practical in assessing human risks involving exposures in the range of study observations."

What OEHHA omits from its Report is that in its 1994 report U.S. EPA unambiguously concluded that the human data are inadequate for quantitative risk assessments. Once again, misrepresentation is not sound science. OEHHA also fails to mention the recent conclusion of WHO/IPCS. That body also stated in unequivocal terms that:

A quantitative risk assessment cannot be conducted on the basis of epidemiological data in which job title was used as a surrogate of exposure Consequently, there are no human data suitable for estimating unit risk. (WHO Diesel Report, p. 254.)

Sample #3 -- On page 2-1 of its report, OEHHA touts the two-day workshop convened in San Francisco in January, 1996 to discuss the use of epidemiologic data for quantitative risk assessments, and asserts that the report "has been updated and revised to reflect the benefit of those discussions."

What the report utterly fails to note, however, is that the one clear conclusion from the San Francisco workshop was that the critical issue of whether Dr. Garshick's studies actually demonstrate a dose-response trend had to be resolved. Indeed, on January 30, 1996, George Alexeeff publicly declared that the Crump/Dawson debate "must be settled." But that debate has not been settled, and OEHHA has refused repeated requests to participate in a forum of the leading bio-statisticians to resolve the debate one way or the other. This clear failure by OEHHA to implement the one overriding consensus of the 1996 workshop should be duly noted in the body of the Report, not consigned to inaccurate footnote discussion in Appendices E and F.

Sample #4 -- OEHHA repeatedly stresses the significance of its "meta-analysis" of 31 epidemiological studies.

What OEHHA does not note in the body of its report, however, is that it excluded 16 of the 47 relevant studies from its meta-analysis. At the very least, OEHHA should discuss fully the impact of this potential selection bias as well as the attendant publication bias. OEHHA also deliberately fails to mention that the two leading meta-analyses of the relevant studies--the meta-analyses conducted by Drs. Stöber and Abel in 1996, and by Drs. Muscat and Wynder in 1995--each concluded that the epidemiological evidence is insufficient to establish diesel engine exhaust as a human lung carcinogen. (See Valberg Report, p. 23.) OEHHA's apparent effort simply to ignore contrary findings is once again not sound science and instead demonstrates bias in this case.

Sample #5 -- OEHHA asserts at pages 1-9 and 6-50 of its report that the relevant epidemiologic studies support a "causal association" between diesel exhaust exposure and human lung cancer.

This is not so. No epidemiological study has ever been published that establishes a causal link between diesel exhaust exposure and human lung cancer. Only studies of statistical association have been undertaken thus far, and these studies are inconclusive since they have not been designed or analyzed to preclude false positives due to multiple comparisons and modelling errors. This very immature state of the scientific knowledge is a critical factor for any meta-analysis to uncover and explain. Yet it passes without mention in OEHHA's highly selective discussion.

IV. The Draft Report Is Invalid

The implementing California statutes (Cal. Health and Safety Code §§39650-39661) require, in part, that the OEHHA Draft Report:

1. "utilize the best available scientific evidence gathered from the public, private industry, the scientific community, and federal, state and local agencies;"
2. "consider all available scientific data, including, but not limited to, relevant data provided by . . . international and federal health agencies, private industry, academic researchers, and public health and environmental organizations;" and
3. be based upon "sound scientific knowledge, methods and practices."

The OEHHA Report fails to clear this threshold by a wide margin. The Draft Report's conclusion that ambient concentrations (2.2 ug/m³) of diesel exhaust will kill more than 2100 people each year in California is directly contrary to the conclusions of the Health Effects Institute and the American Congress of Governmental Industrial Hygienists. (ACGIH has proposed a TLV of 150 ug/m³.) The Draft Report's reliance on the Garshick studies for quantitative risk analysis is directly contrary to the conclusions of U.S. EPA, WHO/IPCS, HEI and Dr. Garshick himself. The Draft Report's reliance on Dr. Mauderly's rat studies for human risk analysis is contrary to the conclusions reached by HEI, CASAC and, most notably, Dr. Mauderly himself. And the Draft Report articulates a unit risk (2 x 10⁻³) that is a full two orders of magnitude greater than that articulated by U.S. EPA and WHO/IPCS (3.4 x 10⁻⁵). In sum, it appears that bias, not sound science, lies at the base of the Draft Report.

The Draft Report also is inconsistent with the conclusions recently articulated in the Report (May 24, 1996) of the Risk Assessment Advisory Committee (RAAC). These conclusions, contained in the RAAC Report, entitled A Review of the California Environmental Protection Agency's Risk Assessment Practices, Policies and Guidelines (hereinafter, the "RAAC Report"), and which must be implemented pursuant to Executive Order W-137-96, include the following:

1. OEHHA should assure consistency with U.S. EPA and other agencies (RAAC Report, pp. ES-6, ES-7, 3-4, 4-7, 4-10);
2. A formalized program for independent external peer review should be developed (RAAC Report, pp. ES-6, ES-8, ES-9, ES-14, 2-4, 2-24, 2-26, 2-27, 3-4, 3-9, 4-6);

3. The Agency needs "further resources" (i.e. lacks expertise) in human health effects and epidemiology. ["epidemiology is not well represented in Cal/EPA"] (RAAC Report, pp. ES-5, ES-12, 2-9);
4. The use of large uncertainty factors when the underlying data are poor should be avoided (RAAC Report, ES-15, 4-6, 4-8);
5. The uncertainties in models, data sets, and parameters and their relative contributions to total uncertainty in a risk assessment should be reported in written risk assessment documents, and when different models may be employed in a risk analysis, perhaps leading to different conclusions, parameter uncertainty should be analyzed at a similar level of detail for all the models (RAAC Report, p. 7-10); and
6. The Agency's "risk characterization practices fall somewhat short of what the profession now considers generally feasible" (RAAC Report, p. ES-16).

The OEHHA Draft Report runs afoul of each of these mandates and as a result falls short of the RAAC's recommendations which are in the process of being codified. Here, too, the OEHHA document misses the mark.

Finally, the Draft Report is inconsistent with recent decisions within the Ninth Circuit Court of Appeals. For example, in Daubert v. Merrell Dow Pharmaceuticals, Inc., 43 F.3d 1311, 1318 (9th Cir. 1995), the court found that one means of showing that a report is based on scientifically valid principles is to demonstrate "that the research and analysis supporting the proffered conclusions have been subjected to normal scientific scrutiny through peer review and publication." The OEHHA Draft Report cannot satisfy this criterion. Indeed, as EMA has noted separately to ARB, the unreasonable timing and overly short review period provided in advance of the July 1 workshop seem calculated to evade peer review, not foster it as required by RAAC.

The Ninth Circuit has also concluded in Daubert at 1321, that "for an epidemiological study to show causation . . . the relative risk . . . arising from the epidemiological data will, at a minimum, have to exceed 2." See also Hall v. Baxter Health Care Corp., 947 F. Supp. 1387, 1403 (D. Or. 1996), where the district court stated that:

The threshold for concluding that an agent was more likely the cause of a disease than not is relative risk greater than 2.0. Recall that a relative risk of 1.0 means that the agent has no effect on the incidence of disease. When the relative risk reaches 2.0, the agent is responsible for an equal

number of cases of disease as all other background causes. Thus a relative risk of 2.0 implies a 50% likelihood that an exposed individual's disease was caused by the agent.

As supposedly confirmed by OEHHA's own "meta-analysis" the relative risk at issue here is approximately 1.43, well short of the minimum requisite 2.0 level of causation. Consequently, OEHHA's assertion that there is a causal association between diesel exhaust exposure and lung cancer will not withstand judicial scrutiny. It also will not withstand scrutiny under the standards articulated by the scientific community. For example, Dr. Frank Speizer, a co-author of the Garshick et al. (1988) cohort study, has emphasized the importance of finding a relative risk of 2.0 or more when investigating respiratory cancers. Writing in 1986, he states,

"Because of the overwhelming effect of cigarette smoking, population-based studies that report on environmental effects, particularly at relatively low levels of excess risk (RR greater than 1.0 but less than 2.0), and that do not attempt to take cigarette smoking into account, must be considered seriously flawed. These studies, therefore, can contribute very little to our understanding of risk factors for respiratory cancer" (Speizer, 1986, Environmental Health Perspectives, 70:9-15, p. 9).

Courts within the Ninth Circuit also have found that in order for animal studies to be sufficient to prove causation in humans, "there must be good grounds to extrapolate from animals to humans, just as the methodology of the studies must constitute good grounds to reach conclusions about the animals themselves." Hall v. Baxter Health Care Corp., 947 F. Supp. at 1397. Moreover, "extrapolations of animal studies to human beings are generally not considered reliable in the absence of a scientific explanation of why such extrapolation is warranted." Id. at 1410. Here, as evidenced by the more recent findings and conclusions of Dr. Mauderly, as well as those of CASAC, there are no good grounds to extrapolate from the relevant animal studies to humans. Consequently, the Draft OEHHA Report will fail on this basis as well.

V. Conclusion

Instead of pursuing a course of action that clearly is not based on sound science and that seems destined to lead to protracted and contested proceedings, OEHHA should actually utilize the best available scientific evidence and conclude that, at this time, a reliable quantitative risk assessment for the constituent(s) of diesel exhaust is simply not possible. That being said, EMA remains willing to participate in and sponsor appropriate studies to advance our knowledge of the subject to the point where quantitative risk assessments could be feasible. We already have undertaken efforts with HEI to pursue that objective. We encourage OEHHA also to participate in these efforts and make the necessary revisions to the Draft Report such that scarce resources can be allocated to further research instead of further confrontations.

**OEHHA's Assessment of Diesel Exhaust
Lacks a Balanced Interpretation
of the Scientific Evidence**

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Executive Summary

In May 1997, the California Environmental Protection Agency (CalEPA) released their revised draft document, "*Proposed Identification of Diesel Exhaust as a Toxic Air Contaminant.*" The current draft document, authored by the Agency's Air Resources Board (ARB) and Office of Environmental Health Hazard Assessment (OEHHA) incorporates changes from their first document, released in 1994. Our report critically evaluates CalEPA's risk assessment and response to public comments in support of the proposed designation of diesel exhaust as a toxic air contaminant (TAC). Specifically, we address several issues where OEHHA does not present a balanced discussion and interpretation:

- **Human Evidence of Carcinogenicity.** We discuss OEHHA's use of the 1987 and 1988 Garshick *et al.* studies and OEHHA's recalculation of quantitative risk estimates (Chapter 7, Appendices E and F, Part B, OEHHA). We also examine the validity and usefulness of the OEHHA's meta-analysis of occupational studies (Appendix D, Part B, OEHHA).
- **Role of a Genotoxic Mechanism of Action.** We review studies cited by OEHHA (Chapters 3 and 5, Part B, OEHHA) supporting their view that diesel exhaust particulate is genotoxic.
- **Probability of Threshold of Response.** We discuss OEHHA's justification for using linear dose-response models based on genotoxic and non-genotoxic mechanisms of action (Chapters 6 and 7, Part B, OEHHA).
- **Extrapolation from Rats-to-Humans.** We reiterate the inappropriateness of using the rat inhalation bioassay for extrapolating responses in rats to humans (Chapter 7, Part B, OEHHA). We also respond to OEHHA's criticisms (Appendix C, Part B, OEHHA) of our showing that the diesel-exhaust potency from rat studies lacks applicability to humans because the studies predict an (unrealistic) lung-cancer risk in carbon black workers.

OEHHA uses results reported by Garshick *et al.* (1987; 1988) to quantitatively estimate the risk of lung cancer associated with exposure to diesel exhaust. We conclude that the Garshick *et al.* 1987 results cannot be used because data on the actual levels of diesel exhaust for the workers studied do not exist. Our reanalysis of the 1988 Garshick *et al.* data reveals a **flat** or even **declining** dose-response relationship. This problem of the dose-response relationship was noted after the release of OEHHA's 1994 report. In apparent response to this problem, OEHHA omitted one group of railroad employees - shopworkers - from its 1997 analysis. However, OEHHA does not justify the omission of this group of

employees. We also maintain that the failure to control for smoking behavior in the 1988 study and inadequate control of smoking in the 1987 study renders the results from both studies uninterpretable.

OEHHA's meta-analysis of the epidemiological literature to qualitatively assess the relationship between diesel exposure and lung cancer does not establish this relationship. Evaluation of OEHHA's analysis reveals evidence of publication bias. Moreover, OEHHA incorrectly omits studies that the Office claims are biased by the "*healthy worker effect*." This effect is most likely not relevant in the context of lung cancer, which has a long latency period. Inclusion of the omitted studies would depress the strength of OEHHA's estimated association between diesel exhaust exposure and lung cancer risk. In addition, none of the studies included in OEHHA's analysis evaluates the influence of actual diesel exhaust concentration on lung cancer risk. Instead, these studies rely on duration of employment as an exposure metric. Use of this metric is problematic because employment duration may be associated with other factors.

OEHHA attempts to strengthen its case for the association between exposure to diesel exhaust and an increased risk of lung cancer by arguing that adsorbed organic compounds on diesel exhaust particles are bioavailable and bioactive. However, the studies cited by OEHHA do not establish bioavailability because they do not demonstrate that genotoxins are released from diesel particles, and the presence of urinary markers and DNA adducts have not shown an association with measurements of diesel exhaust exposure. These studies also failed to control for other sources and routes of exposure to PAHs and nitro-PAHs. Moreover, if the mutagenic activity remains with the diesel particle, OEHHA does not speculate on how PAHs or nitro-PAHs physically reach the peripheral blood cells to form adducts and how PAH or nitro-PAH metabolic products enter the urine.

Because OEHHA must estimate risks associated with much lower diesel exhaust exposures than those directly observed in either occupational epidemiological studies or in rat bioassay studies, OEHHA must establish that the dose-response relationship between exposure to diesel exhaust and the risk of lung cancer is linear. However, OEHHA fails to support this assertion. First, OEHHA has not established that adsorbed genotoxic compounds are bioavailable and bioactive. Moreover, OEHHA's reliance on the analysis by Gaylor and Zheng (1995) suggesting a linear dose-response for non-genotoxic carcinogens is not appropriate since the Gaylor and Zheng analysis is theoretical and is not based on mechanisms that

are likely to be operative in the rat-inhalation bioassay. Furthermore, experimental data demonstrate a threshold for responses mechanistically related to particle-induced tumorigenesis in the rat model.

Finally, we argue that OEHHA should not use the lung tumor data from rats chronically exposed to high levels of diesel exhaust to estimate lung cancer unit risk. For insoluble particles, the lung tumor response is rat-specific and not particle-specific. Other rodents exposed to insoluble particles do not develop lung tumors, and epidemiologic studies of workers exposed to insoluble particles do not report an excess of lung cancer.

The justification for the identification of diesel exhaust as a TAC depends on the estimated risk incurred by the general public after a lifetime exposure to ambient levels of diesel exhaust. However, OEHHA's unit risk estimates are seriously flawed for the following reasons:

- **The epidemiologic studies were not designed to be used for risk assessment purposes. The existence of any dose-response remains problematic. We do not have adequate information on exposure and smoking in worker populations exposed to diesel-engine exhaust. With such low relative risks, it is essential that exposure data be available and that confounding variables be controlled.**
- **A mechanism of action for the proposed carcinogenicity of diesel exhaust in humans has not been identified. In rats, it appears the diesel exhaust-induced tumorigenesis is mediated by non-genotoxic mechanisms that exhibit a threshold. The evidence for genotoxic mechanisms for diesel exhaust is speculative and cannot be used to justify linear-dose models.**
- **The rat is an outlier and exhibits a non-specific response to concentrations of inhaled particulate that lead to lung overload. This finding has been shown repeatedly and has led several scientific advisory groups to discount the rat inhalation bioassay for assessing human cancer risk.**

We conclude that if OEHHA had accepted the scientific uncertainty associated with the diesel exhaust studies and had prepared a more balanced document, then they could not have logically reached the conclusions that they have reported.

1 Introduction

In June 1994, the California Environmental Protection Agency (CalEPA) released a draft document (OEHHA, 1994) evaluating the toxic potential of diesel exhaust and the possible identification of diesel exhaust as a toxic air contaminant (TAC). The current draft document, "*Proposed Identification of Diesel Exhaust as a Toxic Air Contaminant*" (dated May 1997) incorporates comments received during the public comment period (June 1994 - December 1994) and during two public workshops held in September 1994 and January 1996. The current CalEPA document is co-authored by the staff from the Air Resources Board (ARB) and the Office of Environmental Health Hazard Assessment (OEHHA) and consists of an Executive Summary, Part A (Exposure Assessment), Part B (Health Assessment), and Part C (response to public comments). Our report focuses on how discussions in Part B and staff responses in Part C are used by the Agency to reach the conclusions identified in the Executive Summary.

In the Executive Summary (p. 12), CalEPA states,

"The report concludes that a reasonable and likely explanation for the increased rates of lung cancer observed in the epidemiological studies is a causal association between diesel exhaust exposure and lung cancer."

Although text in the Health Assessment Document (Part B) seems reasonably balanced with respect to presenting the relevant data, OEHHA's interpretation and application of the various results are more readily apparent in the Response to Public Comments (Part C). That is, the reasoning by which OEHHA translates the information contained in Part B to the Executive Summary can, in fact, be found in their responses to public comments.

In the current, 1997 draft document, CalEPA relies more heavily on epidemiologic studies than on the animal studies in forming their conclusion on the health risks of diesel exhaust. OEHHA provides results of their own meta-analysis of 31 occupational studies. OEHHA also reaffirms their belief that the studies by Garshick and co-workers provide reliable data for quantitative risk assessment. After revising several parameters from their 1994 report, the Office calculated new unit risks for diesel exhaust.

After the release of their 1994 draft document, OEHHA was heavily criticized during the comment period on its use of the rat inhalation bioassay, on its neglect of the importance of lung overload, and its lack of consideration of a threshold in the rat model system. OEHHA (1997, p. 11, Part C) acknowledges,

"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 [technical support document] 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."

By acknowledging that a lung-overload phenomenon is probably not operative in diesel-exhaust-exposed humans, OEHHA (p. 3, Part C) is necessarily reduced to justifying genotoxic mechanisms as being plausible in the causation of lung cancer by diesel exhaust:

"The possibility cannot be excluded that genotoxicity due to the PAH and nitro-PAH 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."

OEHHA (p. 6, Part C) draws on three areas of investigation to support their contention,

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

To bolster their argument for genotoxic mechanisms of action, OEHHA selected certain studies examining: (1) the extraction of mutagens from diesel particles by physiological fluids, (2) the bioavailability and metabolic activation of particle-associated organics, and (3) the presence of lymphocytic DNA adducts in humans occupationally exposed to diesel exhaust.

After proposing genotoxic mechanisms as providing a link between diesel exhaust and lung cancer, OEHHA then makes several statements regarding carcinogenic potential. First, it is usually assumed that genotoxic carcinogens do not exhibit a threshold of response; thus, OEHHA justifies the

use of linear dose-response models for their risk assessment. Second, the Office uses the genotoxic potential of the adsorbed organic compounds to differentiate diesel exhaust particulate from carbon black particles and coal dust. By distinguishing diesel exhaust from these other particles, OEHHA argues that it is inappropriate to use rat-to-human extrapolations from other particle types to test the validity of extrapolating from rats-to-humans with diesel exhaust exposure.

Our report critiques the following issues in the OEHHA document, where OEHHA lacks a balanced discussion and interpretation:

- **Section 2. Human Evidence of Carcinogenicity:** We discuss OEHHA's use of the 1987 and 1988 Garshick *et al.* studies and OEHHA's recalculation of quantitative risk estimates (Chapter 7, Appendices E and F, Part B, OEHHA). We also examine the validity and usefulness of OEHHA's meta-analysis of occupational studies (Appendix D, Part B, OEHHA).
- **Section 3. Role of a Genotoxic Mechanism of Action:** We review studies cited by OEHHA (Chapters 3 and 5, Part B, OEHHA) supporting their view that diesel exhaust particulate is genotoxic.
- **Section 4. Probability of Threshold of Response:** We discuss OEHHA's justification for using linear dose-response models based on genotoxic and non-genotoxic mechanisms of action (Chapters 6 and 7, Part B, OEHHA).
- **Section 5. Extrapolation from Rats-to-Humans:** We reiterate the inappropriateness of using the rat inhalation bioassay for extrapolating responses in rats to humans (Chapter 7, Part B, OEHHA). We also respond to OEHHA's criticisms (Appendix C, Part B, OEHHA) of our showing that the diesel-exhaust potency from rat studies lack applicability to humans because the studies predict an (unrealistic) lung-cancer risk in carbon black workers.

2 Human Evidence of Carcinogenicity

This section discusses two main flaws in OEHHA's analysis of the epidemiology data. First (Section 2.1, below), the epidemiological studies used by OEHHA to quantify lung cancer risks associated with diesel exposure (Garshick *et al.*, 1987; 1988) do not demonstrate a positive relationship between the incidence of lung cancer and exposure to diesel, as measured in terms of time and concentration. In fact, as noted in an earlier round of comments, re-analysis of the data indicates that even substantial increases in exposure do not increase lung cancer risk. Moreover, Garshick *et al.* (1988) did not control for the effect of smoking, seriously compromising OEHHA's conclusions drawn from this study.

Second (Section 2.2, below), OEHHA's meta-analysis of epidemiological diesel exposure studies does not establish the Office's claim that there is a preponderance of evidence supporting the positive relationship between diesel exhaust exposure and lung cancer.

Section 2.3 summarizes our main conclusions on OEHHA's use of the epidemiology.

2.1 The Garshick *et al.* Data do not Show a Positive Dose-Response Relationship

OEHHA describes two calculations of the incremental cancer risk associated with a $1 \mu\text{g}/\text{m}^3$ increase in average lifetime exposure to diesel exhaust. We critically evaluate both the estimate calculated using the Garshick *et al.* (1987) case-control data (section 2.1.1) and the estimate calculated using the Garshick *et al.* (1988) cohort data (Section 2.1.2).

2.1.1 OEHHA Risk Estimate Calculated Using the Garshick *et al.* (1987) Case-Control Data

OEHHA (1997) uses the results from Garshick *et al.*'s case-control study (1987) of railroad workers along with computations carried out by McClellan *et al.* (1989) to calculate a unit risk estimate (incremental risk per average lifetime exposure to diesel exhaust in $\mu\text{g}/\text{m}^3$).

Garshick *et al.* (1987) matched each of 1,256 lung cancer deaths identified from 15,059 death records for former railroad workers in the United States with two control cases. The control cases were

drawn from the same set of 15,059 death records, and were matched with cases having nearly the same birth and death dates. The cause of death for each control was listed as a “*specified natural cause with no mention of cancer on the death certificate*” (pp. 7-15 Part B, OEHHA). Logistical regression that controlled for the effect of age, asbestos exposure, and smoking history suggested that the risk of lung-cancer increased by 1.648% for each year of exposure to diesel exhaust (as assumed from years of employment).

McClellan computed the incremental risk of lung cancer per μg -year of exposure to diesel exhaust by assuming that workplace diesel exhaust concentrations were $125 \mu\text{g}/\text{m}^3$ or $500 \mu\text{g}/\text{m}^3$, and by correcting for exposure frequency in an occupational setting (40 hours per week, 5 days per week, 48 weeks per year). McClellan used the Garshick *et al.* (1987) result of 1.648% increased risk per year to compute the incremental risk of lung cancer per lifetime average exposure to $1 \mu\text{g}/\text{m}^3$ diesel exhaust. Assuming that occupational diesel exhaust concentrations were $125 \mu\text{g}/\text{m}^3$, the incremental unit risk came out to 1.16×10^{-3} ; assuming that occupational diesel exhaust concentrations were $500 \mu\text{g}/\text{m}^3$, the incremental unit risk came out to 2.90×10^{-4} .

There are three problems with OEHHA’s interpretation of the results from this study. First, the study does not provide a quantitative estimate of risk because exposure was not measured. Second, the results from the Garshick *et al.* 1987 study do not support the downward extrapolation of risks to exposure levels typical of non-occupational exposures. Third, Dr. McClellan has declared to CARB that his quantitative estimates are no longer valid.

2.1.1a Garshick *et al.* (1987) Does Not Provide a Basis for Quantitative Risk Assessment

OEHHA’s analysis of Garshick *et al.* (1987) computes risk as a function of employment duration in the railroad industry. That is, the computation does not assess the relationship between risk and diesel exhaust concentration, a value that is assumed to be constant across all workers during their employment in this industry. In Section 2.1.2, we demonstrate that changes in diesel exhaust concentration appear to be unrelated to changes in risk. The relative risk identified may therefore represent the risk associated with some factor associated with duration of employment in the railroad industry other than exposure to diesel exhaust. For example, levels of environmental tobacco smoke (ETS) in the railroad industry may

have been elevated relative to other occupations. Also, the dichotomous classification of smokers vs. non-smokers is likely to allow considerable residual confounding from smoking.

In short, the analysis of Garshick *et al.* (1987) data does not show a relationship between exposure to diesel exhaust and the risk of lung cancer, but instead shows a relationship between lung cancer risk and employment duration (and with whatever factors “employment duration” may be correlated). The failure of the Garshick *et al.* (1988) cohort data (discussed in Section 2.1.2) to establish an association between diesel exhaust concentration and lung cancer risk supports the hypothesis that some other factor is responsible for the relative risk quantified on the basis of the Garshick *et al.* (1987) case-control study.

At the very least, because the diesel exhaust exposure concentrations assumed by OEHHA in its derivation of a unit risk are completely hypothetical, the unit risk results cannot be regarded as quantitative estimates. Even if exposure to diesel exhaust were associated with some level of increased risk of lung cancer, OEHHA’s analysis of the Garshick *et al.* (1987) case-control data is not a valid estimate of this risk’s magnitude.

2.1.1b OEHHA’s Analysis of Garshick *et al.* (1987) Does not Support Downward Extrapolation of Risks to Levels Below Occupational Exposures

Setting aside the problems due to a lack of actual measurements of diesel exhaust concentration, the Garshick *et al.* (1987) case-control study does not support OEHHA’s attempt to extrapolate risks from occupational levels to much lower non-occupational levels. Garshick *et al.*’s analysis suggests that virtually all of the elevated lung cancer risk is associated with occupational exposures exceeding 20 years. Garshick *et al.* (1987) notes on p. 1244 that “*subjects with ≥ 20 yr. of diesel exhaust exposure had the highest, significantly elevated odds ratio (OR = 1.64; 95% CI = 1.18, 2.29). Subjects with 5 to 19 diesel-years had an odds ratio of 1.02 (95% CI = 0.72, 1.45).*” That is, the risk of lung cancer among workers exposed to diesel exhaust between 5 and 19 years was essentially unchanged, compared to the risk of lung cancer in workers with between 0 and 4 years of diesel exposure.

Let us assume that:

- The relevant measure of dose is the product of incremental diesel concentration above background and duration of exposure;
- The incremental diesel exposure among exposed workers can be estimated as $43 \mu\text{g}/\text{m}^3$ (see Section 2.1.2 of our report or p. 7-18 in OEHHA, 1997, Part B);
- The average exposure duration among workers with between 5 and 19 years of exposure is 12 years (the average of 5 and 19 years), while the average exposure duration among workers with between 0 and 4 years of exposure is 2 years (the average of 0 and 4).

From these assumptions, it follows that the incremental exposure to diesel exhaust among workers with between 5 and 19 years of occupational experience in the railroad industry (in $\mu\text{g}\text{-years}/\text{m}^3$) is (12 years - 2 years) $\times 43 \mu\text{g}/\text{m}^3$, or $430 \mu\text{g}\text{-years}/\text{m}^3$.

OEHHA notes that "*the average annual ambient concentration of diesel exhaust to which Californians are exposed is $2.2 \mu\text{g}/\text{m}^3$...*" (OEHHA, 1997, Part B, pp. 7-28). Multiplying this value by an average life span of 70 years yields $154 \mu\text{g}\text{-years}/\text{m}^3$, far less than the $430 \mu\text{g}\text{-years}/\text{m}^3$ that Garshick *et al.* (1987) indicates is **without elevated risk**. Hence, even if the Garshick *et al.* (1987) results are accepted at face value, they do not support OEHHA's inference that exposure to diesel exhaust is responsible for lung cancer among non-occupationally exposed individuals living in California.

2.1.2 OEHHA Risk Estimate Calculated Using the Garshick *et al.* (1988) Cohort Data

OEHHA's 1997 risk estimate (OEHHA, 1997, Part B) using the Garshick *et al.* (1988) cohort data is similar to the calculation prepared by OEHHA in its June, 1994 Health Risk Assessment for Diesel Exhaust (OEHHA, 1994) with the following important changes:

- OEHHA uses a different estimate of historic exposures;
- OEHHA omits shopworkers from its analysis;
- OEHHA omits cumulative lung burden as a measure of dose.

We first summarize our original analysis of the OEHHA's June, 1994 risk assessment (California EPA, 1994), demonstrating that substantial increases in the Office's own measure of dose are not associated with an increased risk of lung cancer (Section 2.1.2a). OEHHA's 1997 modifications to its 1994 analysis attempt to eliminate this problem. In Sections 2.1.2b, 2.1.2c, and 2.1.2d, we critically evaluate each of these changes (summarized above), demonstrating that they lack foundation. Section 2.1.2e explains that the omission of statistical control for smoking habits in Garshick *et al.* (1988) independently renders the results of this study uninterpretable. Hence, we conclude that, as in 1994, OEHHA's use of the Garshick *et al.* cohort data falls short of showing an association between the risk of lung cancer and exposure to diesel exhaust.

2.1.2a Analysis of the 1994 California EPA Risk Assessment

The 1994 OEHHA risk assessment divides two groups of workers (exposed and unexposed) into four exposure categories based on the length of time they worked in the railroad industry after 1959. OEHHA relies on Garshick *et al.*'s reasoning that exposure to diesel exhaust **prior to 1959** was the same among all exposed workers in the study cohort. Hence, any differences in exposure among members of this cohort reflect differences in work tenure **following 1959**.

For each exposure category, Garshick *et al.* reports the relative risk of lung cancer compared to the corresponding cohort of unexposed workers. For example, the first exposure category includes workers who remained in the railroad industry for up to four years following 1959 (*i.e.*, workers who left the industry between 1959 and 1963). Garshick *et al.* calculated the relative risk of exposure for these workers by comparing them to **unexposed** workers who remained in the railroad industry for up to four years following 1959. The remaining three exposure categories include workers with between 5 and 9 years of railroad employment following 1959, workers with between 10 and 14 years of railroad employment following 1959, and workers with between 15 and 17 years of railroad employment following 1959.

Additionally, Garshick *et al.* reported relative risks using two different definitions of the "exposed" worker cohort. The first set of relative risk values reflects lung cancer prevalence among what Garshick *et al.* refers to as all "exposed" workers. This group includes workers in various job categories thought to expose subjects to diesel exhaust, **including shopworkers**. The second set of

reported relative risk values reflects lung cancer prevalence among all exposed workers, **excluding shopworkers**. Both sets of relative risk values appear in Table 2.1

Table 2.1
Relative Risk of Lung Cancer for Exposed Workers as Reported by Garshick *et al.* (1988)

Years Worked in Railroad Industry After 1959	Relative Risk of Lung Cancer Compared to "Unexposed" ^a Railroad Workers with the Same Job Tenure	
	Exposed Workers, Including Shopworkers ^b	Exposed Workers Excluding Shopworkers ^c
1 to 4	1.20	1.34
5 to 9	1.24	1.33
10 to 14	1.32	1.33
15 to 17	1.72	1.82

Notes:

- a* "Unexposed" railroad workers (e.g., clerks, ticket takers, etc.) were also exposed to diesel exhaust but to a lesser extent than "exposed" railroad workers. The "unexposed" workers served as a benchmark to whom exposed workers were compared.
- b* These relative risk values also appear in Table 7-6 of OEHHA (1994).
- c* These relative risk values also appear in Table 7.8 of OEHHA (1997).

OEHHA used data from Woskie *et al.* (1988a,b), along with anecdotal information about changes in exposure conditions in the railroad industry, to quantify atmospheric diesel concentrations over time. Woskie *et al.* (1988a) report atmospheric diesel concentrations measured in 1983 for various railroad job categories. OEHHA (1994) assumed that historical concentrations equaled contemporary concentrations [*i.e.*, 1983 concentrations reported by Woskie *et al.* (1988a)] multiplied by an exposure factor. Specifically, OEHHA's 1994 analysis assumed that:

- **For shopworkers**, the exposure factor was 0.0 in 1945 and increased linearly to a peak value of 15.0 in 1959. OEHHA inferred the factor of 15.0 from historical measurements of nitrogen dioxide in railroad shops. (To allow for assumed, but not established heterogeneity in shopworker exposure, only one-half were assumed to be exposed at the measured levels.)
- **For other exposed workers**, the exposure factor was 0.0 in 1945, and peaked at 2.0 in 1959.
- **For all exposed workers** (including exposed shopworkers), the exposure factor was 2.0 between 1960 and 1970 and then dropped to 1.0 thereafter.

Figure 7-2 in OEHHA (1994) illustrates the exposure factor functions for shopworkers and other exposed workers, while Figure 7-2 in OEHHA (1997) illustrates the exposure factor function for exposed workers excluding shopworkers (the 1997 document includes only one exposure factor function since, as explained in Section 2.2.1c, OEHHA (1997) excludes shopworkers from consideration). Section 2.1.2b (below) describes in detail the relationship between contemporary (1983) diesel concentrations and historical concentrations assumed in OEHHA's 1997 analysis. In short, OEHHA assumed in 1997 that the ratio of historical concentrations to 1983 concentrations among other exposed workers is somewhat larger than the ratio assumed in OEHHA's 1994 analysis. In contrast, OEHHA assumed in 1997 that the ratio of historical concentrations to 1983 concentrations among exposed shopworkers is substantially smaller than the ratio assumed in OEHHA's 1994 analysis. As we explain in Section 2.1.2b, the 1997 historical exposure assumptions, which lack foundation, eliminate the influence of including or excluding shopworkers from the analysis of the dose-response relationship.

OEHHA's 1994 analysis calculated two measures of incremental exposure for the exposed workers relative to the unexposed workers. The first measure was $\mu\text{g-years}/\text{m}^3$, which was computed by multiplying the area under the exposure factor function by the 1983 atmospheric diesel concentration reported by Woskie *et al.* (1988a). Application of appropriate multiplicative factors to account for occupational exposure frequency and duration yielded a lifetime average exposure in $\mu\text{g}/\text{m}^3$. The second measure is calculated using the first measure, but applies a physiological model to determine the total incremental deposition of diesel exhaust in the lungs for shopworkers and for other exposed workers. OEHHA's 1994 analysis computed exposure for the cohort consisting of all exposed workers and all shopworkers making the assumption that half of the shopworkers were exposed to elevated diesel exhaust concentrations, while the other half of the shopworkers were unexposed.

Plotting the relative risk values reported by Garshick *et al.* against the corresponding exposure measures computed by OEHHA yields two sets of dose response curves (one for exposure measured in terms of lifetime average $\mu\text{g}/\text{m}^3$, and one in terms of lifetime diesel exhaust deposition in the lung (mg)). Our critique of OEHHA's 1994 analysis was straightforward. Because Garshick *et al.* reports two sets of relative risks – one for exposed workers **excluding** shopworkers, and the other for **all** exposed workers and all shopworkers – we computed lifetime exposure for these two groups.¹ These exposure levels

¹ We note here that Gradient's 1994 comments incorrectly excluded unexposed shopworkers from the calculation of exposure for the second of these two cohorts. Nonetheless, our findings remain the same, as described in this section.

appear in Tables 2.2a (measured in terms of average lifetime exposure concentration in $\mu\text{g}/\text{m}^3$) and 2.2b (measured in terms of total lifetime lung burden in mg).² We then compared the dose-response relationships for these two groups, showing that the dose-response relationship is not monotonic.

² Note that, like OEHHA (1994), the calculations in Tables 2.2a and 2.2b are based on the assumption that only 50% of the 12,092 shopworkers are exposed (*i.e.*, 6,046 shopworkers are exposed).

Table 2.2a
Average Incremental Lifetime Exposure to Diesel for the Garshick *et al.* (1988) Cohort:
Average Concentration During Employment in the Railroad Industry Converted to Lifetime
Average Concentration ($\mu\text{g}/\text{m}^3$)

Exposure Category ^a	Exposed Shopworkers N= 6,046 Conc > Backgrnd: <u>102 Tg/m^3</u> Lifetime Avg Exposure (Tg/m^3)			Unexposed Shopworkers N= 6,046 Conc > Backgrnd: <u>0 Tg/m^3</u> Lifetime Avg Exposure (Tg/m^3) ^d	Other Exposed Workers N=29,290 Conc > Backgrnd: <u>43 Tg/m^3</u> Lifetime Avg Exposure (Tg/m^3)			All Exposed Workers and all Shopworkers <u>N=41,382</u> Lifetime Avg Exposure (Tg/m^3) ^e	
	AUC ^b	Un Adjusted ^c	Adjusted ^c	Adjusted	AUC ^b	Un Adjusted ^c	Adjusted ^c	Un Adjusted ^c	Adjusted ^c
1-4 yr.	115.5	168.3	55.5	0	18	11.0	3.6	32.0	10.7
5-9 yr.	124.5	181.4	59.8	0	27	16.6	5.5	37.9	12.6
10-14 yr.	133.5	194.5	64.1	0	36	22.1	7.3	43.6	14.5
15-17 yr.	137.5	200.3	66.0	0	40	24.6	8.1	46.1	15.4

Notes:

- a Garshick *et al.* calculate lung cancer relative risk for the following subsets of his cohort: individuals who continued railroad work for 1 to 4 years after 1959, individuals who continued railroad work for 5 to 9 years following 1959, individuals who continued railroad work for 10 to 14 years following 1959, and individuals who continued railroad work for 15 to 17 years following 1959. OEHHA (1994) approximated exposure for each of these groups by using the midpoint of each of these ranges. For example, OEHHA assumed that individuals who continued railroad work for 10 to 14 years past 1959 worked in the railroad industry from no later than 1945 through 1971.
- b "AUC" is the "Area under the Curve" for the exposure factor (see Figure 7-2 in OEHHA, 1994) between 1945 and retirement. The AUC values in this table appear in columns 2 and 3 of Table 7-8 in OEHHA (1994). The exposure factor function used in the 1997 analysis differs substantially (see Figure 7-2 in OEHHA, 1997, Part B).
- c Unadjusted lifetime average exposure is computed by multiplying the AUC value by the contemporary incremental exposure above background (which yields $\mu\text{g}\text{-years}/\text{m}^3$) and then dividing this result by the average duration of a lifetime (assumed to be 70 years). The adjusted lifetime exposure ($\mu\text{g}/\text{m}^3$) is the unadjusted value multiplied by the product of: 1/2 (proportion of inhalation that takes place at work), 5/7 (number of days at work each week), and 48/52 (number of weeks at work each year) to calculate the adjusted exposure value. The overall product of these factors is 0.33. Hence the unadjusted lifetime average exposure for exposed shopworkers of 168.3 $\mu\text{g}/\text{m}^3$ is 115.5 (AUC) \times 102 $\mu\text{g}/\text{m}^3$ (contemporary incremental exposure above background) \div 70 years (lifetime duration). The adjusted lifetime average exposure of 55.5 $\mu\text{g}/\text{m}^3$ is equal to the unadjusted exposure of 168.3 $\mu\text{g}/\text{m}^3$ multiplied by 0.33.
- d Although the Woskie *et al.* data do not suggest that the shopworkers are a heterogeneous population in so far as diesel exhaust exposures, OEHHA assumed in 1994 that half the shopworkers were "unexposed." The lifetime average exposure for unexposed shopworkers is zero since the incremental diesel exhaust concentration above background for these workers is zero. In their 1997 analysis, OEHHA omits the shopworkers entirely, even though workers for whom exposure was greatest would be expected to provide the greatest "signal" for lung cancer risk.
- e The lifetime average exposure for exposed workers and all shopworkers is the average exposure for exposed shopworkers, other exposed workers, and unexposed shop workers, weighted by the number of individuals in each category.

Table 2.2b
Average Incremental Lifetime Exposure to Diesel for the Garshick *et al.* (1988) Cohort:
Incremental Lung Burden During Employment in the Railroad Industry Converted to Average
Annual Lung Burden^a

Exposure Category	Exposed Shopworkers N= 6,046 Incremental Deposition Above Background (mg) ^b	Unexposed Shopworkers N=6,046 Incremental Deposition Above Background (mg) ^c	Other Exposed Workers N=29,290 Incremental Deposition Above Background (mg) ^d	All Exposed Workers and Unexposed Shopworkers N=41,382 Incremental Deposition Above Background (mg) ^e
1-4 yr.	416.3	0	6.2	65.2
5-9 yr.	655.2	0	10.6	103.2
10-14 yr.	892.7	0	15.0	141.0
15-17 yr.	1052.0	0	17.5	166.1

Notes

- a* Total particle deposition in the lungs of unexposed workers is assumed to be 3.5 mg (1-4 yr.); 4.4 mg (5-9 yr.); 5.5 mg (10-14 yr.); and 7.2 mg (15-17 yr.). Incremental exposures equal total deposition minus these background total deposition values. These values were computed by dividing values in the fourth column of Table 7-9 in OEHHA (1994) (mg*yr for unexposed shopworkers) by the lifetime duration of 70 years.
- b* Computed by dividing the values in column 2 of Table 7-9 in OEHHA (1994) by 70 and subtracting the background exposure values detailed in footnote (a).
- c* Incremental exposure above background for unexposed shopworkers is zero.
- d* Computed by dividing the values in column 3 of Table 7-9 in OEHHA (1994) by 70 and subtracting the background exposure values detailed in footnote (a).
- e* Incremental lifetime average annual deposition above background for all exposed workers and all shopworkers is the average of the incremental deposition for exposed shopworkers, unexposed shopworkers, and other exposed workers, weighted by the number of individuals in each of these groups (i.e., weighted by N).

In the present report, we make the same point as in the 1994 Gradient report, but in a slightly different manner. Specifically, using the relative risk values published by Garshick *et al.* (1988) and the exposure levels computed in Tables 2.2a and 2.2b for the two exposed worker groups, we created four dose-response lines – one for each exposure category (railroad employment up to 4 years following 1959, railroad employment 5 to 9 years following 1959, and so forth). The relative risks for the two sets of exposed workers in each exposure category tended to be similar (compare column entries in Table 2.1 above). However, the exposure levels differed substantially (see Tables 2.2a and 2.2b). Specifically, average exposure among exposed workers **excluding shopworkers** was always substantially less than average exposure among exposed workers **including shopworkers**. Hence, the dose-response lines are, in all four cases, nearly horizontal, or even slightly downward sloping. Figure 2-1 illustrates the four

dose-response lines where exposure is measured in terms of average lifetime exposure concentration in $\mu\text{g}/\text{m}^3$; Figure 2-2 illustrates the four dose-response lines where exposure is measured in terms of lifetime lung burden. In any case, **the Garshick *et al.* results, together with OEHHA's 1994 reconstruction of historical exposure, show no evidence of an association between higher diesel exhaust concentrations and an increased risk of lung cancer.**

As noted at the beginning of this section, OEHHA's 1997 analysis of the Garshick *et al.* cohort data differs in some respects from its 1994 analysis. In an effort to eliminate the "paradox" revealed by the preceding analysis, OEHHA has:

- Re-quantified historic exposure levels so that the exposure levels in the cohort of all exposed workers and all shopworkers do not differ substantially from the exposure levels in the cohort of exposed workers excluding shopworkers. This change has the effect of making the exposure levels for the two groups in each exposure category the same, thus eliminating the horizontal dose-response lines.
- Omitted the shopworkers from the analysis, hence eliminating the right endpoint of each of the dose-response lines in Figures 2-1 and 2-2.
- Omitted analysis of the exposure in terms of total lung-deposited diesel exhaust – the exposure measure that offered the most dramatic illustration of the absence of an upward-sloping, dose-response relationship (see Figure 2-2).

Sections 2.1.2b, 2.1.2c, and 2.1.2d challenge the validity of these changes to OEHHA's analysis.

2.1.2b OEHHA's New Estimate of Historic Exposures Lacks Adequate Foundation

We identify two problems with OEHHA's new estimates of historic exposure to diesel exhaust among railroad workers. First, compared to its 1994 analysis, OEHHA has, with no explanation, increased the peak exposure (achieved in 1959) among the cohort of exposed railroad workers excluding shopworkers by 50%. Second, OEHHA has implicitly decreased the assumed peak exposure level for exposed shopworkers, again without adequate explanation or justification (other than the fact that the results better fit the desired conclusion). The effect of these changes is to make the calculated average historic exposure to diesel exhaust among exposed railroad workers insensitive to the inclusion or exclusion of shopworkers from this cohort, thus eliminating the paradox we described in our Section 2.1.2a.

OEHHA explains the basis for its 1994 estimate of historic diesel exposures in Section 7.3.5 of OEHHA (1994). Of particular interest are the second and third paragraphs in that section. Here, OEHHA infers historic diesel concentrations based on *“limited historical data on nitrogen dioxide levels in railway repair shops.”* OEHHA continues, *“These data showed that in the era designated ‘pre-ventilation’ (1950-1959) the average level (based on 22 measurements at four locations) was 10 times the average measurement for 1983 (based on 238 measurements)...”* Using this information, OEHHA concludes that for shopworkers, *“The exposure factor for 1945-1960 was taken to increase linearly from zero to a peak value of 15× in 1960”* (pp. 7-14). For other exposed workers, OEHHA assumes that diesel exposure increases from 0 in 1945 to twice current levels in 1960 (see pp. 7-15 in OEHHA, 1994).

For its revised analysis, OEHHA takes up the issue of historic exposures in Section 7.3.2.2.2 of OEHHA (1997). The extent to which historic diesel concentrations exceed contemporary levels is addressed in the final paragraph of that section. Here, OEHHA states that, *“For train workers, the exposed group in the present calculation, the linear rise from 0 in 1945 is assumed to peak at 3 times the 1983 level at the beginning of 1959...”* (pp. 7-17). OEHHA explains that, *“The exposure factor of 3 is a scaled down version of the factor of 10 that Woskie et al. (1988b) reported for exposure of railroad shopworkers to nitrogen dioxide.”* We note that **OEHHA does not explain why its 1997 analysis assumes a peak exposure concentration for exposed railroad workers excluding shopworkers that exceeds contemporary levels by a factor of 3, while its 1994 analysis assumes peak levels exceeded historic levels by a factor of 2.** Moreover, the *“factor of 10”* reported by Woskie et al. (1988b) specifically applied to **repair shops**. OEHHA does not justify why a “scaled down” version of the Woskie et al. (1988b) factor of 10 should be used.

Even more dramatic is OEHHA’s most recent revision of assumptions regarding exposure of shopworkers. In the fifth item in its discussion of sources of uncertainty in its 1997 analysis (Section 7.3.3), OEHHA (1997) asserts that its exclusion of shopworkers from its analysis does not substantially affect its results. Specifically, OEHHA states that, *“If ... the proportion of unexposed shopworkers is set at 0.5 ... then the overall risk for the shopworkers would be about the same as for the train workers. With these assumptions, this finding of Garshick et al. on the effect of excluding shopworkers would be within random variation...”* (OEHHA, 1997, Part B, pp. 7-21).

Assuming that half the shopworkers are exposed and the other half are unexposed, OEHHA's assertion that the overall risk for shopworkers is the same as for other exposed workers can hold only if one assumes that the area under the "exposure factor" curve multiplied by the incremental contemporary exposure for exposed shopworkers ($102 \mu\text{g}/\text{m}^3$) is only twice the corresponding value for other exposed workers (for whom the incremental contemporary exposure is $43 \mu\text{g}/\text{m}^3$). Because the ratio of $102 \mu\text{g}/\text{m}^3$ to $43 \mu\text{g}/\text{m}^3$ is 2.37, this condition implies that the area under the exposure factor curve for shopworkers must be less than the corresponding area for other exposed workers. Specifically, the area under the exposure factor curve for exposed shopworkers must be only 84.3% of the area under the exposure factor curve for other exposed workers ($2.0 \div 2.37$). This condition is in direct contradiction to the only empirical evidence available (the nitrogen dioxide measurements cited in OEHHA's 1994 document).

OEHHA provides no evidence or reason to explain why the ratio of the areas under the exposure factor curves for shopworkers vs. other exposed workers is now less than unity, compared to OEHHA's 1994 estimated ratio, which greatly exceeded unity³. The absence of such an explanation renders OEHHA's 1997 analysis of the Garshick *et al.* cohort data invalid.

2.1.2c OEHHA's Omission of the Shopworkers from the Analysis Lacks Adequate Foundation

Section 2.1.2a of our report notes OEHHA's omission of the shopworkers from consideration in its 1997 analysis of the Garshick *et al.* cohort data. In Section 7.3.3 of its 1997 analysis (fifth item), OEHHA states that

"it was prudent to exclude [shopworkers] from some of the analyses. This assumption was made because of the great heterogeneity of exposures in the very broad classification of shopworker. Many of the shopworkers were in shops near the engines [sic] sheds, which had the very high exposures when engines were running without modern ventilation systems. Other shopworkers were in facilities not subject to diesel exposures... There does not seem to be any useful information on the proportion of shopworkers in the unexposed or lesser exposed shops (pp. 7-21, emphasis in original)."

³ The ratio of the area under the exposure factor curve for exposed shopworkers to the area under the exposure factor curve for other exposed workers in OEHHA's 1994 analysis ranges from a maximum value of 7.5 (for workers terminating employment in 1960) to a minimum value of 3.17 for workers terminating employment in 1980 (see Figure 7-2 in OEHHA, 1994). Assuming that 50% of shopworkers are unexposed, the corresponding ratio comparing the AUC for all shopworkers to the AUC for other exposed workers would range from a maximum of 3.75 ($50\% \times 7.5$) to a minimum of 1.58 ($50\% \times 3.17$).

The singling out of shopworkers by OEHHA (1997) as a group whose historical exposure is unacceptably uncertain lacks adequate explanation. Certainly, historical exposure among all groups of workers, including, for example, engineers, brakemen, and so forth, is uncertain. OEHHA does not explain what level of uncertainty is acceptable (hence warranting the inclusion of exposed workers other than shopworkers), and what level of uncertainty is uncertain (hence warranting the exclusion of the shopworkers). Without such criteria, the exclusion must be considered to be arbitrary.

Contemporary data in Woskie *et al.* (1988b) indicate that shopworker exposure to diesel exhaust is relatively **homogenous**. Woskie *et al.* (1988b) divided the railroad worker cohort into five career exposure groups (clerk, signal maintainer, engineer/firer, braker/conductor, and shop), each of which consisted of one or more job groups. For example, “shop” consisted of three job groups – electricians, machinists, and supervisor/laborer/other shopworkers. The Tukey-Kramer multiple comparison test found that although there were no significant differences in exposure within groups ($p < 0.05$), “*A single factor ANOVA model using career group as the explanatory variable for the log of the ARP [Adjusted Respirible Particulate] concentration found career group was a [sic] significant ($p = 0.00001$) in explaining the variations in ARP exposures ($R^2 = 0.25$)*” (p. 398)⁴. In fact, an examination of the shop exposure data in Table I of Woskie *et al.* (1988b) reveals that the coefficient of variation (sample mean \div standard error of the mean) for each job group is on the order of 5% to 15%. Moreover, these results are based on a substantial number of observations – 176 shopworkers in all. Mean exposure concentrations among shopworker job groups (125 to 157 $\mu\text{g}/\text{m}^3$) substantially exceed levels among the next most highly exposed group, brakemen/conductors (83 to 95 $\mu\text{g}/\text{m}^3$). Woskie *et al.* (1988b) conclude that, “*Although we suspect that there are differences within the career groups, they are small enough that more sampling would be needed to resolve them*” (p. 401).

Even if it is assumed that exposure among shopworkers were heterogeneous, and that there is no readily available data quantifying the proportion of shopworkers who were “exposed” vs. “unexposed,” OEHHA’s decision to drop this group from the analysis remains unwarranted. As shown in Section 2.1.2b of our report, even if it is assumed that half the shopworkers were **unexposed** (an “*unbiased*”

⁴ There is one exception: the freight conductor/hostler comparison within the braker/conductor career group yielded statistically significant differences.

estimate in the absence of information” (p. 7-21), according to OEHHA, Part B, 1997), the inclusion of the shopworkers in the dose-response analysis has a substantial effect on the results.

OEHHA’s response to this issue (OEHHA, 1997, Part C), as it was raised in our public comments in 1994, does not adequately address this issue. OEHHA responds to this issue on p. C-OEHHA-2 (in response to comment 1) and on p. C-OEHHA-15 (in response to comment 19). The first response (p. C-OEHHA-2) makes several claims:

- *“As pointed out in the TSD [technical support document (OEHHA, Part B, 1997)], a substantial proportion of the shopworkers was not **exposed** to diesel exhaust”* (emphasis in original). The OEHHA (1997) report asserts that shopworker exposure was heterogeneous. As far as we can tell, however, the report never even claims that a “substantial proportion” of these workers were unexposed. At the very least, no documentation or analysis is presented supporting this assertion.
- *“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.”* As discussed in Section 2.1.2b, shopworker exposure is very likely to substantially **exceed** exposure among other exposed workers (and hence, risk among exposed shopworkers should greatly exceed other exposed workers if diesel exhaust is a carcinogen). In fact, as pointed out in Section 2.1.2b, historical exposure among shopworkers (exposed and unexposed) equals historical exposure among other exposed train workers only if the ratio of historical exposures to contemporary exposures among exposed shopworkers is **less than** the corresponding ratio for other exposed train workers. Such a claim is inconsistent with empirical evidence that has been gathered on this issue (specifically, the nitrogen dioxide measurements).
- *“On this basis, the very small reduction of risk with shopworkers removed, as reported in Garshick et al. (1988), is well within the random variation of the data.”* As just demonstrated, there is no basis for this comment.
- *“OEHHA staff were unable to replicate the three-fold and eight-fold increases in estimated risk suggested by the comment.”* Tables 2.1, 2.2a, and 2.2b detail our derivation of a dose-response relationship for exposure measured both in terms of $\mu\text{g}/\text{m}^3$ and in terms of lung-deposited diesel exhaust. Figures 2-1 and 2-2 demonstrate that the dose-response relationship does not show a positive association between diesel exposure and the risk of lung cancer. It is this finding that invalidates OEHHA’s conclusions.

OEHHA’s second set of responses (p. C-OEHHA-15) to this issue is likewise inadequate. OEHHA claims:

- “As pointed out in the TSD, a substantial proportion of the shopworkers was not exposed to diesel exhaust.” We addressed this point above.
- “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.” Whether or not this is true does not address the comment to which this text responds.
- “OEHHA staff were unable to replicate the three-fold and eight-fold increases in estimated unit risk suggested by the comment.” We addressed this point above.
- “There is not enough information on the shopworkers to support a contradiction of the analysis of other data from the Garshick *et al.* (1988) cohort.” We disagree. As discussed earlier, only by making a number of highly implausible assumptions – assumptions that contradict the only available empirical data (the nitrogen dioxide measurements) – is it possible to dismiss the absence of dose-response relationship made apparent the inclusion of the shopworker data.
- “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.” Again, even if exposure were highly variable, a broad range of assumptions regarding its nature yields a dose-response curve inconsistent with OEHHA’s hypothesis that diesel exhaust causes lung cancer in humans.

Given the importance of the shopworker data, OEHHA’s justification for the proposed regulation should demonstrate that historic exposures among this group (including both exposed and unexposed shopworkers) were low enough to conclude that inclusion of these workers in the analysis does not have a statistically significant effect on the calculated dose-response relationship. Short of a quantitative analysis demonstrating this point, it must be concluded that OEHHA’s omission of the shopworkers from its analysis is a *post hoc* adjustment. Such an adjustment eliminates important information mitigating against the claim that the Garshick *et al.* cohort data demonstrate a positive dose-response relationship between diesel exhaust exposure and lung cancer.

2.1.2d OEHHA’s Omission of the Cumulative Lung Burden Exposure Lacks Explanation

OEHHA’s omission from its 1997 analysis of cumulative lung burden as a measure of exposure lacks adequate explanation, especially given the prominent role that measure of exposure played in OEHHA’s 1994 analysis. As far as we can tell, OEHHA offers only two explanations for this change. In the last paragraph of Section 7.2.3 (OEHHA, Part B, 1997, p. 7-2), OEHHA states that “*lung burden was*

not used to calculate risk estimates from human study data because the human exposures used in the calculations are not considered great enough to result in sufficient human lung burden to require use of a lung burden model.” If this is the case, then OEHHA should state what levels of exposure are great enough to warrant use of this model. Outside reviews could then better understand the rationale for this change.

OEHHA’s second explanation for omission of the lung burden model, which appears in its response to comments document (OEHHA, 1997, Part C), states in response to comment 19 (p. 2-OEHHA-15) that “*quantifying ... [lung burden] is highly problematic and the new version of the TSD (Section 7.3) does not attempt to estimate lung burden in humans.*” However, OEHHA does not explain what factors complicate use of the model now, in contrast to its previous application in OEHHA's 1994 report.

As OEHHA’s 1994 analysis presented lung burden as a plausible measure of exposure, and, given that this measure of exposure provides an even more striking illustration of the non-monotonicity of the dose-response data based on the Garshick *et al.* cohort data (Garshick *et al.*, 1988), OEHHA should provide a coherent rationale for now dropping this measure.

2.1.2e OEHHA’s Analysis of Garshick *et al.* (1987) does not Provide an Adequate Basis for Dismissing Smoking as a Confounder

Although the Garshick *et al.* (1988) cohort study did not control for the effect of smoking, OEHHA (1997) claims that this omission is not important because the Garshick *et al.* (1987) case-control study established that failure to control for cigarette smoking does not substantially affect estimates of relative risk. We believe that the failure to control for smoking invalidates inferences drawn from either study.

It is well established that smoking elevates the relative risk of lung cancer. The landmark 1964 Report of the Surgeon General determined that the risk of lung cancer among male smokers exceeded the corresponding risk among non-smokers by factor of approximately 10 (Brandt, 1990). Because smoking has such a substantial influence on the risk of lung cancer, Dr. Frank Speizer, a co-author of the Garshick

et al. (1988) cohort study, has emphasized the importance of controlling for this factor when investigating other potential risk factors for this disease. Writing in 1986, he states,

“Because of the overwhelming effect of cigarette smoking, population-based studies that report on environmental effects, particularly at relatively low levels of excess risk (RR greater than 1.0 but less than 2.0), and that do not attempt to take cigarette smoking into account, must be considered seriously flawed. These studies, therefore, can contribute very little to our understanding of risk factors for respiratory cancer” (Speizer, 1986, p. 9).

By this reasoning, the Garshick *et al.* (1988) cohort study is flawed because it does not control for cigarette smoking and because the relative risks reported are less than 2.0.

OEHHA (1997) attempts to rely on the Garshick *et al.* (1987) case-control study results to justify the validity of the Garshick *et al.* (1988) cohort results, even in the absence of controlling for smoking. However, the results from the case-control study indicate that its statistical control for smoking were inadequate. The Garshick *et al.* (1987) case-control study reports both the crude relative risk of lung cancer among workers with over 20 years of occupational exposure to diesel exhaust (relative risk = 1.39), and the corresponding risk ratio value that has been adjusted for exposure to asbestos and for lifetime smoking, measured in pack-years (relative risk = 1.41). That is, adjusting for smoking and exposure to asbestos had no effect on the relative risk associated with long term diesel exposure.

The minimal difference between crude and adjusted relative risk values would not be unexpected if the prevalence of smoking among both the cases and controls were the same. In fact, members of the case cohort smoked more than members of the control cohort. As detailed in Table 3 of Garshick *et al.* (1987), 80% of the cases smoked, while only 73% of the controls smoked. Among cases 32% were classified as having no more than 50 pack-years of smoking, while 43% were classified as having more than 50 pack-years of smoking. The corresponding figures for the controls were 38% and 30%⁵.

As there are more smokers among the cases, failure to control for smoking would be expected to result in a **higher** relative risk than after adjustment, but the reported result goes in the opposite direction. If, as Garshick *et al.* (1987) claim, long term exposure to diesel exhaust is associated with an

⁵ The remaining cases and controls were either non-smokers (9% for cases, 11% for controls) or could not be classified (23% for cases and 22% for controls).

increased risk of lung cancer, then failure to control for smoking should have increased the estimated “crude” risk ratio for this parameter. Because it did not, there is reason to believe that either long term diesel exposure is not associated with the risk of lung cancer, or Garshick *et al.* (1987) did not adequately control for smoking. In any case, the finding by Garshick *et al.* (1987) that the unadjusted crude risk ratio and the adjusted risk ratio for diesel exposure were nearly identical does **not** justify OEHHA’s lack of concern regarding statistical control of smoking in its 1997 analysis of the Garshick *et al.* (1988) cohort study.

Stober and Abel (1996) outline additional problems with relying on the Garshick *et al.* (1987) case-control study results to address the lack of control for smoking in the Garshick *et al.* (1988) cohort study. They state (p. S-38),

“The cohort study by Garshick et al. (1988) has received particular attention because the authors maintained that they had dealt with the question of the effect of the subjects’ smoking habits. However, the investigation on smoking habits to which they refer (Garshick et al. 1987b) is very unsatisfactory. Firstly, the proportion of smokers found in this study was unusually high ($\geq 80\%$); secondly, it related only to employees more than 50 years old; and thirdly, the proportion of smokers was derived only from 50 asbestos-exposed railroad workers and their 192 controls, with just a simple differentiation being made between smokers and nonsmokers. In any case, the information on smoking is by no means adequate so that, judged by the quality criteria previously established by one of its own co-authors (Speizer, 1986), the study must be regarded as seriously flawed.”

2.2 OEHHA’s Meta Analysis Does not Establish a Relationship Between Diesel Exposure and Lung Cancer

Although the meta-analysis conducted by OEHHA includes some 31 studies and 40 estimates of the magnitude of the relative risk of lung cancer associated with exposure to diesel exposure, there are several problems with the analysis that cast doubt on the inference drawn by OEHHA. Perhaps the most important problem compromising OEHHA’s meta-analysis is evidence of publication bias combined with the use of statistical methodology that provides more weight to small, imprecise studies. This problem is discussed in Section 2.2.1. Second, without adequate justification, OEHHA dismisses a number of studies yielding low relative risk estimates based on the assertion that the risk estimates from these studies were depressed by the healthy worker effect. We discuss this problem in Section 2.2.2.

Finally, in Section 2.2.3, we point out that the meta-analysis fails to provide an estimate of risk associated with changes in atmospheric diesel exhaust concentrations.

Before proceeding, we note several **other reviews** of the epidemiological literature investigating the association between diesel exhaust and lung cancer. Upon review of studies published through June of 1993, Cohen and Higgins (1995) concluded that *“exposure to diesel exhaust in a variety of occupational circumstances is associated with small to moderate relative increases in lung cancer occurrence and/or mortality”* (p. 269). However, even Cohen and Higgins find the epidemiological data inadequate to support a quantitative estimate of risk, stating, *“Although these data provide relative rankings of exposure, the absence of concurrent exposure information is the key factor that limits interpreting the epidemiologic findings and using them to make quantitative estimates of cancer risks”* (p. 6). Other reviewers found that the epidemiological literature does not support even a qualitative association between diesel exhaust exposure and lung cancer. An extensive review of this literature by Stober and Abel (1996) concluded that, *“there is no causal relationship between diesel exhaust inhalation and lung cancer”* (p. S-41). They continue, stating that, *“At present... it can be subsumed from the cohort studies that no definite increase in lung cancer risk from diesel emissions has so far been demonstrated epidemiologically. And there is certainly not any good evidence of a dose-effect relationship”* (p. S-41). Muscat and Wynder reviewed 14 case-control or cohort studies. They state that, *“Using common criteria for determining causal associations, the epidemiologic evidence is insufficient to establish diesel engine exhaust as a human lung carcinogen”* (Muscat and Wynder, 1995, p. 812).

2.2.1 Likely Publication Bias Invalidates OEHHA’s Meta-Analysis

As OEHHA (1997, Part B) notes on p. D-4, *“Publication bias, or the increased likelihood or preference for the publication of statistically significant results compared to nonsignificant or null results, may potentially distort a pooled risk estimate.”*

To assess the potential presence of publication bias, OEHHA creates two “funnel graphs” – one for case-control studies, and one for cohort studies. A funnel graph plots risk estimates (specifically, the log of the relative risk estimate) from each study against its sample size. In the absence of publication bias, all studies of a given sample size provide risk estimates that are symmetrically distributed about the

central estimate of risk. Among studies with smaller sample sizes, this spread is greater due to the greater influence of stochastic error.

Plotting the sample size on the vertical axis and the risk estimate on the horizontal axis, the funnel plot should, in the absence of publication bias, produce a plot that forms a triangle with a peak directly above the center of the base of the triangle. OEHHA's funnel graphs appear in Figures D-6 and D-7 of OEHHA (1997). Curiously, OEHHA claims – with no supporting quantitative analysis – that the graphs provide no evidence of publication bias. Tables 2.3 and 2.4 (below) quantitatively summarize the results of these two graphs, showing that, among smaller studies, the central estimate of risk is larger than it is among larger studies. In other words, it appears that among the smaller studies, smaller risk estimates (or even relative risk estimates less than unity) are “missing” from the body of published literature.

Table 2.3
Quantitative Summary of the Case-Control Funnel Graph (Figure D-6) in OEHHA (1997)

Sample Size	<u>Log Relative Risk – Number of Studies</u>							Approx. Average Log RR	Median Log RR
	-0.3 to -0.2	-0.2 to -0.1	-0.1 to 0.0	0.0 to 0.1	0.1 to 0.2	0.2 to 0.3	0.3 to 0.4		
0-100	1	0	0	1	2	1	4	0.19	0.25
100-200	0	0	0	2	0	0	1	0.15	0.05
200-300	0	0	0	0	3	0	0	0.15	0.15
300-400	0	0	0	0	2	0	0	0.15	0.15
400-500	0	0	0	0	1	0	0	0.15	0.15
500-600	0	0	0	0	0	0	0	NA	NA
600-700	0	0	0	1	0	0	0	0.05	0.05

Table 2.4
Quantitative Summary of the Cohort Funnel Graph (Figure D-7) in OEHHA (1997)

Sample Size	<u>Log Relative Risk – Number of Studies</u>								Approx. Average Log RR	Median Log RR
	-0.2 to -0.1	-0.1 to 0.0	0.0 to 0.1	0.1 to 0.2	0.2 to 0.3	0.3 to 0.4	0.4 to 0.5	0.5 to 0.6		
0 to 5,000	1	0	0	2	2	1	1	1	0.25	0.25
5,000 to 10,000	1	1	1	1	0	0	0	0	0.0	0.0
10,000 to 15,000	0	0	0	0	1	0	0	0	0.25	0.25
15,000 to 20,000	0	0	1	0	0	0	0	0	0.05	0.05
20,000 to 25,000	0	0	0	0	0	0	0	0	NA	NA
25,000 to 30,000	0	0	0	0	0	0	0	0	NA	NA
30,000 to 35,000	0	0	1	0	0	0	0	0	0.05	0.05
35,000 to 40,000	0	0	0	1	0	0	0	0	0.15	0.15
40,000 to 45,000	0	0	0	1	1	0	0	0	0.20	0.20

The suggestion of potential publication bias is particularly evident for the case-control studies, as the average log risk ratio drops from 0.19 for studies with between 0 and 100 subjects to 0.05 for the largest study (between 600 and 700 subjects); the corresponding median log risk ratio drops from 0.25 to 0.05. These results should be viewed in light of the fact that, using the random effects model (which yields higher risk estimates), the pooled risk ratio estimate for the case-control studies was 1.43 (OEHHA, 1997, Part B, Table D-3), while for cohort studies, the pooled risk ratio estimate of 1.25 (OEHHA, 1997, Part B, Table D-3). That is, the case-control studies, which show the greatest potential for publication bias, are precisely those studies that suggest the largest risk ratio for the association between lung cancer and exposure to diesel exhaust.

Although OEHHA does not explicitly admit the possibility of publication bias, the Office does acknowledge that that “*there is a lower density of studies in the lower left portion of figures D.6 and D.7, indicating fewer small, statistically insignificant studies.*” OEHHA does not explain how this observation is consistent with the assertion that there is no evidence of publication bias.

Finally, we note that the random effects model that yields the higher pooled estimates of relative risk (see the pooled entries for cohort studies and case-control studies at the top of Table D-3 in OEHHA, 1997, Part B) places greater weight on smaller studies – the very studies that are more likely to be subject to publication bias (because stochastic error can yield high risk estimates, yet low risk estimates may not be published due to the lack of the statistical significance). As OEHHA (1997) states on p. D-10, “*Concern about publication bias is more acute in random-effects than fixed-effects models, as the former tend to weight studies more evenly.*” Note that the fixed-effect pooled-risk estimate for cohort studies of 1.01 barely exceeds unity (see OEHHA, 1997, Part B, Table D-3).

In summary, despite OEHHA’s assertions to the contrary, publication bias appears to have affected the pool of studies available for the meta-analysis detailed in Appendix D (OEHHA, 1997, Part B). This bias is particularly pronounced for case-control studies, which yield the highest pooled-risk estimate.

2.2.2 OEHHA’s Dismissal of Studies Because of the Alleged Healthy Worker Effect Lacks Foundation

OEHHA (1997) defines the “healthy worker effect” (HWE) as the “*manifestation of selection bias related to hiring and retention of workers who are typically healthier than the general population, resulting in spuriously lower risk estimates for a variety of illnesses, including those potentially related to occupational exposures*” (p. D-8). OEHHA reports that the pooled relative-risk estimate calculated using the fixed-effect model was, as expected, smaller among studies OEHHA labeled as exhibiting the HWE (0.99) than it was among those studies OEHHA labeled as **not** exhibiting this effect (1.49).

Although the HWE may be important in the context of some illnesses, it is unlikely to affect studies of illnesses with long latency periods – like lung cancer. Simply put, the “less healthy” workers – *i.e.*, those that develop cancer – do not develop the illness until late in life and hence will not be excluded

from the study cohort by hiring and retention practices. In fact, if employers or employees can predict long-term cancer risks, their diagnostic acumen should be the subject of intense study.

Because it is unlikely that the HWE substantially affects the analysis of the relationship between exposure to diesel exhaust and the development of lung cancer, OEHHA has not demonstrated that those studies it believes is affected by this phenomenon should be discounted. Hence, the pooled estimate of 0.99, referred to above, cannot be easily dismissed, contradicting OEHHA's conclusions.

2.2.3 OEHHA's Meta-Analysis Fails to Address the Relationship Between Diesel Exhaust Concentration and the Development of Lung Cancer

OEHHA suggests that because the vast majority of studies used duration of employment to quantify diesel exposure that exposure assessment was adequate. This measure does not distinguish among workers exposed to different concentrations of diesel exhaust. It also fails to rule out some other factor that is coincident with time. Problems related to ignoring differences in exposure concentrations were discussed at length in Section 2.1.2b in the context of the Garshick *et al.* (1988) cohort study of U.S. railroad workers. In that case, there was an increased risk of lung cancer associated with time employed in the railroad industry. However, risks did **not** increase as a function of time-averaged exposure concentration. Similar phenomena may have affected the studies included in OEHHA's meta-analysis.

2.3 Conclusion

OEHHA relies on epidemiological studies to quantify the risk of lung cancer associated with exposure to diesel exhaust. Specifically, OEHHA estimates the incremental risk of lung cancer from the case-control study conducted by Garshick *et al.* (1987) and the cohort study conducted by Garshick *et al.* (1988). The Garshick *et al.* case-control study cannot be used to quantify risk because empirical measurements of exposure concentrations do not exist. The absence of this information also compromises inferences drawn about the existence of a relationship between diesel exhaust exposure and lung cancer, because the study only establishes an association between lung cancer and duration of employment in the railroad industry.

Use of the Garshick *et al.* (1988) cohort study to quantify the risk of lung cancer associated with diesel exposure also is invalid. Using the relative risks reported by Garshick *et al.* (1988) and historic exposure values calculated by OEHHA (1994), our analysis reveals a flat, or even **declining**, dose-response relationship. In OEHHA's current draft report (1997), the Office changed several parameters from their 1994 unit-risk calculations. Our biggest concern is the elimination of the shopworker population in their 1997 analyses. OEHHA's exclusion of the shopworkers from their analyses yields the appearance of an upward-sloping, dose-response relationship. However, OEHHA's rationale for exclusion of this group is not consistent with the literature. In contrast to OEHHA's claim that heterogeneity among the exposure of shopworkers makes its inclusion of that group in the analysis inadvisable, Woskie *et al.* (1988b) report that, as a group, shopworker exposure to diesel exhaust far exceeded the exposure for other job categories, and that variation in exposure among shopworkers was limited.

In addition, the results from the Garshick *et al.* (1988) cohort study are uninterpretable because this study did not control for smoking. OEHHA claims that controlling for smoking is unnecessary in the 1988 cohort study based on an analysis of the effect of smoking in the 1987 case-control study. However, the application of statistical controls for smoking in the 1987 study were inadequate. Smoking remains a confounder in both of the Garshick *et al.* studies and cannot be dismissed.

Finally, OEHHA's meta-analysis of the epidemiology literature to qualitatively assess the relationship between diesel exhaust exposure and lung cancer is flawed. First, funnel analysis indicates that the results have been substantially affected by publication bias. Second, OEHHA incorrectly dismisses studies that it claims have been biased by the "healthy worker effect," a phenomenon unlikely to be relevant for lung cancer. Third, none of the studies included in OEHHA's analysis addresses the relationship between lung cancer and diesel exhaust **concentration**. Rather, these studies establish an association between lung cancer and employment duration, a quantity that is sensitive to other factors that change with time both in the exposed (or case) cohort as well as in the unexposed (or control) cohort.

OEHHA has failed to identify any epidemiologic evidence establishing a clear dose-response relationship between diesel exhaust exposure and lung cancer. Many other reviews of the literature investigating whether there is a causal relationship between diesel exhaust and lung cancer conclude that

the epidemiologic data are quantitatively inadequate (U.S. EPA, 1994; Health Effects Institute, 1995; Muscat and Wynder, 1995; Stober and Abel, 1996; World Health Organization, 1996). The studies were not designed for risk-assessment purposes, and their limitations must be accepted; OEHHA should acknowledge that it is not possible to quantify a hypothetical risk associated with exposure to diesel exhaust. Hence, OEHHA lacks a basis for establishing that ambient levels of diesel exhaust are a health risk to the California population.

3 Role of a Genotoxic Mechanism of Action

3.1 Extraction of Adsorbed Organic Compounds

In section 5.1.2.6 *Extraction Under Physiological Conditions*, OEHHA discusses those studies investigating the ability of physiological media to remove particle-bound organic material. The Office notes the **failure** of simulated body fluids to remove bound mutagens (Brookes *et al.*, 1981; King *et al.*, 1981; Siak *et al.*, 1981). In other studies, the addition of protein (Clark and Vigil, 1980) or macrophages (King *et al.*, 1983) **decreased** the mutagenic potential of the organic fraction extracted by solvents. OEHHA then discusses the work by Wallace *et al.* (1987) and Keene *et al.* (1991), who demonstrated an increase in mutagenicity after incubation with a phospholipid emulsion. Although Part B acknowledges that the methodology used by Wallace, Keene, and coworkers differs from other similar types of studies, OEHHA emphasizes repeatedly the importance of the Wallace, Keene, and coworker studies, when the Office addresses public comments about bioavailability.

The interpretation of the results from Wallace *et al.* (1987) and Keene *et al.* (1991) is problematic. First, Wallace *et al.*, (1987) used scraped aged, accumulated soot from an exhaust pipe as their source of diesel particulate, which is different from particulate in fresh, airborne diesel exhaust. Second, both Wallace *et al.* (1987) and Keene *et al.* (1991) prepared samples and reported mutagenicity in a peculiar manner. The suspended particles were subjected to sonication and agitation, the effects of which on particle size and surface properties are unknown. In addition, sonication and agitation do not simulate physiological processes. Third, in both investigations, after incubation with the emulsion, the investigators separated the particles from the media and observed that the mutagenicity resided with the particulate fraction and not the filtered supernatant. That is, the emulsion was **not** effective in extracting the organic material off the diesel particles. The authors suggested that the phospholipid emulsion acted to “*solubilize*” the adsorbed components. Because the bioactivity resided in the particle fraction, it is unclear what the authors meant when they used the term “*solubilize*”. The relevance of their test system to the *in vivo* situation remains to be explored and validated, and it is inappropriate for OEHHA to rely prematurely on these studies. For example, if the lungs are not under overload conditions (as OEHHA suggests), and macrophages are not impaired in their ability to take and remove particles, and organic material is not released from the particles by lung surface fluids, then it is difficult to imagine how lung epithelial cells are at risk of exposure to mutagenic organic compounds.

3.2 Bioavailability and Metabolic Activation

In Part C, OEHHA (p. 6, Part C) refers repeatedly to

“...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).

Turning to section 3.4 of Chapter 3, Part B, OEHHA briefly and uncritically presents results from the studies by Kanoh *et al.* (1993) and by Scheeper *et al.* (1994).

Kanoh *et al.* (1993) conducted a short-term rat study to assess the use of urinary 1-hydroxypyrene as a marker of PAH exposure. Rats were exposed to 4.2 mg/m³ diesel exhaust for 7 hr/day, 5 day/week, for 8 weeks. Urine samples were collected, and 1-hydroxypyrene was measured 2, 4, and 8 weeks after the exposure ended. The pyrene content in the diesel particulate was 36.0 ng/mg. The authors reported an increase in urinary 1-hydroxypyrene levels, peaking at 4 weeks post-exposure. However, the concentration of pyrene contained in the rodents' food was 9.0 ng/g, and the authors did not properly account for the relative contribution of inhaled and ingested pyrene in the diesel-exposed and sham-exposed animals. First, the authors calculated that the daily dose of pyrene inhaled was 24.77 ng and ingestion was 135 ng. However, for the calculation of inhalation, the authors used airborne concentration of diesel particulate and not the deposition fraction. Therefore, pyrene values for inhalation should be 12% to 20% of 24.77 ng, that is, only 3 to 5 ng. Second, the authors implied that the two groups of rats consumed the same amount of food, but it does not appear that the authors measured food consumption. Mauderly *et al.* (1994) reported lower body weights in rats exposed to 2.2 or 6.0 mg/m³ diesel exhaust than in sham-exposed rats. In Kanoh's short-term study, it is conceivable that food consumption could have increased in a compensatory manner after particle exposures ended. Without actual measures of food consumption, the authors cannot assume that the particle-exposed rats ingested the same amount of pyrene-containing food as the control rats. Because of the overestimation of inhaled pyrene and possible underestimation ingested pyrene, we disagree that exposure to diesel exhaust was a significant factor in the reported differences. Even if food consumption did not increase, and even if all the pyrene adsorbed to diesel particles were bioavailable, diesel exhaust-derived pyrene only accounted for about 2-3 % of the daily pyrene dose.

Scheeper *et al.* (1994) measured the concentration of urinary 1-aminopyrene in 3 diesel train-engine mechanics and 2 office clerks. Ambient levels of total suspended particulate matter (TSPM) and respirable suspended particulate matter (RSPM) were measured in the repair shop and office. Airborne 1-nitropyrene levels were determined from the collected TSPM. Urine was collected over a 24-hr period on Sunday, Monday, and Tuesday. The authors reported that the cumulative and average excretion of 1-aminopyrene when days are combined (that is, Monday and Tuesday or Sunday, Monday, and Tuesday) were greater in the train mechanics than in the office clerks; however, when the authors compared daily excretion levels on a single-day basis, there were no differences between the two groups of employees. Relating these findings to diesel-engine particulate exposure is problematic. The authors reported that *“a considerable part of the APM [airborne particulate matter] is not primarily derived from diesel exhaust.”* Furthermore, TSPM and RSPM levels were not consistent with the time and frequency of engine test runs. In addition, in the mechanics, the highest 24-hour average of urinary 1-aminopyrene occurred on Monday, but airborne levels of 1-nitropyrene were not detectable. The authors provide no information on other sources of nitro-PAHs to which mechanics may have been exposed. The authors did state that this was a preliminary study, and should be treated as such when drawing conclusions about bioavailability.

In section 5.1.2.6 of Chapter 5, Part B, OEHHA mentions the study by Schenker *et al.* (1990), in which urinary mutagenicity was not correlated with exposure to diesel exhaust in 87 railroad workers. The authors obtained measurements of RSP, using personal monitors, and corrected these values for exposure to environmental tobacco smoke. Given the fact that OEHHA appears to be trying to assess the bioavailability of mutagens in section 3.4, Chapter 3, Part B, OEHHA should have also discussed the negative findings of Schenker for railroad workers.

3.3 Presence of DNA Adducts

OEHHA (p. 5, Part B) refers to the presence of lymphocytic DNA adducts in persons occupationally exposed to diesel exhaust as supporting

“...the results of epidemiologic studies which describe a positive correlation between human diesel exposure and the induction of lung cancer.”

OEHHA cites the studies by Hemminki *et al.* (1994), Hou *et al.* (1995), and Nielson *et al.* (1996), who investigated DNA adduct levels in peripheral blood cells from healthy, non-smoking males. The subjects were employed as bus garage workers, bus mechanics, or truck terminal workers. It should be noted that the two studies by Hemminki *et al.* (1994) and Hou *et al.* (1995) are on the same workers, who presumably were measured on two occasions. In the first report (Hemminki *et al.*, 1994), the bus garage workers (n = 16), but not the bus mechanics (n = 23), had higher lymphocytic DNA adduct levels than control workers (n = 22); in the second publication, both garage workers and mechanics showed higher DNA adduct levels. *Hprt* mutation frequencies, however, were similar in “exposed” and control persons. Truck terminal workers were evaluated only in the first report and their mean adduct levels were higher than in the control workers. It is very important to stress that exposure to diesel exhaust was presumed and no measurements were taken. In addition, garage workers and mechanics are exposed to diesel fuel during refueling and lubricating oils during engine overhauls; thus, the potential for dermal exposure to PAHs exists and was not taken into account in their analyses. Finally, although data were collected on various social and personal factors, these data were not included in any of the analyses.

Nielsen *et al.* (1996) also examined bus garage workers and bus mechanics. In contrast to the findings of Hemminki, Hou, and coworkers, Nielson observed higher adduct levels in the mechanics than in the garage workers. Again, diesel exhaust concentrations were not measured, so exposure can only be assumed. In fact, the authors state,

“Inspection of the working environment gave no indication of significant air pollution from DE, as the garages were very well ventilated and precautions were taken to avoid exposure to engine exhaust.”

Both groups of workers were, however, exposed to lubricating oil. The authors, unlike OEHHA, did not appear to over interpret their findings.

“This study demonstrated that bus garage workers and mechanics were exposed to a higher level of genotoxic compounds compared to a nonoccupationally exposed control group...The source of genotoxins was unclear as well as the route of exposure, but there were indications pointing towards PAH from DE in ambient air and used lubricating oil...The study indicated that skin absorption of PAH might be an important factor to consider when studying PAH exposure from air pollution sources.”

3.4 Conclusion

OEHHA relies heavily on several studies to justify the interpretation that adsorbed organic compounds on diesel exhaust particles are bioavailable and bioactive. However, these studies do not demonstrate that genotoxins are released from diesel particles, and the presence of urinary markers and DNA adducts have not been coupled to measurements of diesel exhaust. Furthermore, other sources and routes of exposure to PAHs and nitro-PAHs have not been controlled. Finally, if the mutagenic activity remains with the diesel particle, OEHHA does not speculate on how PAHs or nitro-PAHs physically reach the peripheral blood cells to form adducts and how PAH or nitro-PAH metabolic products enter the urine.

4 Probability of Threshold of Response

4.1 Genotoxic Carcinogens

When justifying the use of linear dose-response models, OEHHA refers to the commonly used practice of assuming the absence of a no-effect level for genotoxic carcinogens. Thus, their assertion that the adsorbed organic compounds are bioavailable and bioactive has important implications for their risk calculations. As noted above, we do not find their cited evidence for *in vivo* genotoxicity persuasive.

4.2 Non-genotoxic Carcinogens

OEHHA cites the analysis by Gaylor and Zheng (1996), which suggests that linear extrapolation is appropriate even for non-genotoxic carcinogens. That is, OEHHA relies on the possibility that non-genotoxic carcinogens do not exhibit a threshold of response (Chapter 6, Part B, OEHHA). OEHHA's dependence on Gaylor's and Zheng's analysis is not justified for several reasons.

Gaylor and Zheng analysis is theoretical and is supported by only one experimental example. The authors use a formula relating tumor incidence to cell kinetic parameters and show that, indeed, "insignificant" (*i.e.*, less than 20%) changes in cell proliferation could result in significant increases in tumor incidence. Although their calculations are internally consistent, they derive from a theoretical model, and should not be used as evidence of linearity for dose-response.

It does not appear that it was the intention of Gaylor and Zheng to validate their model, and they provide only one example to support their theory. The authors cite the studies of Maronpot *et al.*, (1993) and Kociba *et al.* (1978) who evaluated the effects of tetrachlorodibenzo-*p*-dioxin (TCDD) in female Sprague-Dawley rats. According to Gaylor and Zheng, 125 ng TCDD/kg/day did not affect the proliferation of hepatocytes (Maronpot *et al.*, 1993), but 100 ng TCDD/kg/day did increase the incidence of hepatocellular carcinomas (Kociba *et al.*, 1978). However, these results were reported from two different groups of investigators and with such a close dose range (that is, 100 and 125 ng TCDD/kg/day), it would be essential that the study design and experimental methods be identical between the two laboratories before Gaylor and Zheng can conclude that increases in tumor incidence occurred at lower doses than increases in cell proliferation.

Gaylor's and Zheng's (1995, p. 221) theory is based on the premise that

“a threshold dose is questionable if a nongenotoxic carcinogen acts via a cell receptor. Also, a nongenotoxic carcinogen that increases the cell proliferation rate, via the cell division rate and/or cell removal rate by apoptosis, by augmenting an existing endogenous mechanism is not likely to have a threshold dose.”

However, the authors also state (Gaylor and Zheng, 1995, p. 221),

“Nongenotoxic cytotoxic carcinogens that increase cell proliferation rates to replace necrotic cells are likely to have a threshold dose for cytotoxicity below which necrosis and hence, carcinogenesis do not occur. Thus, low dose cancer risk estimates based upon nonthreshold, linear extrapolation are inappropriate for this situation.”

The current theory for particle-induced tumorigenesis in the rat-inhalation bioassay includes a component of inflammation (Driscoll, 1996). While these inflammatory cells may induce increases in cell proliferation via the production of growth factors and other bioactive components, they also are capable of increasing cell proliferation via cell injury. Inflammatory cells also produce oxidants, which in turn, form DNA adducts. Furthermore, the presence of adequate quantities of anti-oxidants are protective against oxidant-induced mutations.

Results from Driscoll's laboratory and Mauderly's laboratory demonstrate that a threshold does exist for rat-lung responses linked to particle-induced tumorigenesis. In Mauderly's 1987 diesel exhaust study, which OEHHA used for their unit risk calculations, rats exposed to 3.5 mg/m³ or 7.0 mg/m³ diesel exhaust developed lung tumors, but rats exposed to 0.35 mg/m³ did not. In addition, those animals exposed to the lowest concentration of diesel exhaust did not exhibit any biochemical or cytological changes in their bronchoalveolar lavage fluid or lung tissues (Henderson *et al.*, 1988). The authors concluded (p. 546),

“The results suggest that, for the noncarcinogenic health effects reported in this paper, there is a threshold of exposure below which adverse effects were not observed.”

Driscoll and coinvestigators have examined the inflammatory and mutagenic responses of rats exposed to varying concentrations of α -quartz, carbon black, or titanium dioxide (Driscoll *et al.*, 1996,

1997). At particle levels that did not elicit marked inflammation, *hprt* mutations in epithelial cells did not occur. The investigators (Driscoll *et al.*, 1997, p. 107) concluded,

“Specifically, lung doses of non-genotoxic particles that do not produce inflammation, or elicit a degree of inflammation which can be dealt with by lung defenses, may not increase the risk of mutation (and possible lung tumors). That some degree of inflammation may be tolerated without increasing mutation frequency is supported by the results of the present studies...Overall, these findings indicate that inflammation may play a key role in the in vivo mutagenic effects of particle exposure. Importantly, a role, in whole or in part, for particle-elicited inflammatory cells in the mutagenic effects supports a non-linear relationship between particle exposure and in vivo mutation.”

4.3 Conclusion

OEHHA has not adequately justified the use of a linear dose-response. They have not established that adsorbed organic compounds are bioavailable and bioactive. OEHHA's reliance on the analysis by Gaylor and Zheng (1995) suggesting a linear dose-response for non-genotoxic carcinogens is not appropriate. Gaylor and Zheng analysis is theoretical and is not based on mechanisms that are likely to be operative in the rat-inhalation bioassay. Furthermore, experimental data demonstrate a threshold for responses mechanistically related to particle-induced tumorigenesis in the rat model.

5 Extrapolation from Rats-to-Humans

5.1 The Rat as an Outlier

The lung tumor response in rats is not particle specific. The development of lung tumors in rats exposed to diesel exhaust is no different than the response observed in rats after lifetime lung overburdening with other particulates such as carbon black, titanium dioxide, talc, iron oxide (rust), and volcanic ash (see Mauderly and McCunney, 1994). That is, laboratory rats respond to the lifetime lung overburden of particulate, and not specifically to diesel exhaust.

Because only rats, and not mice and hamsters, develop lung tumors after chronic inhalation of high levels of a variety of insoluble particles, most scientists are of the opinion that rats have an anomalous response to inhaled, insoluble particles of any kind. Contrary to OEHHA's statement that the results in mice are "*mixed*," Dr. Heinrich and Dr. Stober, both premier researchers in this field, came to dramatically different conclusions in their comments on OEHHA's 1994 draft. Specifically, Dr. Heinrich states (p. 67, Part C, OEHHA):

"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."

Dr. Stober states (p. 145, Part C, OEHHA):

"[The LARC analysis] removes any significance from the mouse studies."

Finally, Dr. Mauderly, another eminent researcher in the particle inhalation area, has published, with his colleagues, a thorough study of diesel exhaust exposure in CD-1 mice, which concludes (Mauderly *et al.*, 1996):

"The lack of an exposure-related increase of primary lung neoplasms among CD-1 mice exposed chronically to diesel exhaust contrasts with the significant increase observed in F344 rats exposed concomitantly using the same methods and concentrations."

Thus, OEHHA's characterization of the mouse results as "*mixed*" contrasts sharply with the accepted opinions of the research community.

OEHHA does not adequately address the fact that rats have an anomalous response to the inhalation of particles. The sequelae of particle retention in the rat lung are exaggerated in that species, and, consequently, the lung tumors that develop are not relevant to other species of animals or to humans. Specifically, when rats inhale high levels of particles over extended periods of time, the following mechanisms come into play:

- Lung overload (lung overburdening of particles, resulting in reduced rates of clearance for deposited particles).
- Exaggerated influx of inflammatory cells (both macrophages and neutrophils) into the lungs. Rat neutrophils, in and of themselves, have been shown to be tumorigenic in rat lungs.
- Inadequate levels of lung antioxidants (diminished levels of oxygen free-radical scavengers).
- Alveolar Type II cell epithelial hyperplasia.

Because these observations coincide with lung tumor development in rats, toxicologists propose that they relate mechanistically to rat lung tumorigenesis. Research is currently underway to elucidate the reasons behind the peculiar response in rats. In humans, even at large lung burdens, we do not know, if in fact, alveolar clearance is impaired. In humans occupationally exposed to inert particles, there is no evidence indicating an exaggerated influx of neutrophils or alveolar type II cell hyperplasia (Watson and Valberg, 1996). Most importantly, none of these steps have been shown to be a consequence of diesel-exhaust particle inhalation in humans.

In concordance with these differences in biologic response between rats and humans, the epidemiology of workers exposed to inhaled, insoluble particles has not identified an excess lung cancer risk. Workers occupationally exposed to carbon black, either in its manufacture or use, have been evaluated in a number of epidemiologic studies. Because historical exposures to carbon black in the work environment were known to be elevated, study of these workers provides a good test of possible

increases in lung cancer risk. Yet, data from the carbon-black manufacturing industries in the US and the UK do not establish an excess risk of lung cancer (Valberg and Watson, 1996).

Inhalation of insoluble, low-toxicity particulates by other occupational groups has not resulted in excess cancer risk. These groups include TiO₂ workers (Chen and Fayerweather, 1988), workers exposed to nonasbestiform talc (Wergeland *et al.*, 1990), workers exposed to iron oxide (Stokinger, 1984), and coalworkers (National Institute for Occupational Safety and Health, 1986; Mauderly, 1994; IARC, 1997). Coalworkers, in particular, in earlier times are known to have accumulated large burdens of lung-retained coal particles (which are primarily composed of carbon), yet this worker population does not exhibit excess lung cancer risk. IARC recently evaluated inhaled coal dust as ranked it as "Group 3" (unclassifiable as to carcinogenicity in humans due to a lack of evidence of carcinogenicity from either animal or human studies).

Contrary to the position of CalEPA/OEHHA, regulatory bodies in the U.S. have recognized the anomalous response of rats to the inhalation of large quantities of insoluble particles.

- The Clean Air Scientific Advisory Committee (CASAC) is a peer-review group for U.S.EPA composed of experts in inhalation toxicology. CASAC (1995) determined that the response of rats to inhaled diesel exhaust particles is **not** useful for U.S.EPA in developing cancer unit risks (that is, for human health risk assessment). CASAC (1995) states:

"The cancer-causing mechanism in the rat may be unique to the rat and does not appear to occur in other species including humans. The mechanism in rats is apparently related to particulate overload followed by a sequence of events beginning with inflammation and ending in tumorigenesis. These events are conditional upon particle overload which also occurs in rats exposed to high concentrations of inert dusts as well. Consequently, it appears that these studies are not relevant for human risk assessment."

- In another context, the U.S.EPA (U.S.EPA, 1988) addressed the fact that chronic inhalation of TiO₂ results in lung tumors in rats. U.S.EPA delisted TiO₂, from the toxics release inventory, as a lung carcinogen because,

"in the rat bioassay, the dose levels of TiO₂ used overwhelmed the normal clearance mechanisms of the lungs" and "the overall weight-of-evidence determination shows there is not sufficient evidence to reasonably anticipate that TiO₂ will cause cancer in humans."

- The Presidential/Congressional Commission on Risk Assessment and Risk Management (CCRARM) expressly identified in a 1996 draft document (and again in the 1997 final report) some of the mechanisms and substances that are **not** predictors of human health effects. CCRARM (1997) singled out the response of rat lungs to inhaled particulates (giving carbon black and TiO₂ as examples) for which inhalation studies, positive for lung tumors in rats, are not likely to be predictive of human cancer risk.

In spite of this wide-spread opinion that the rat inhalation bioassay for insoluble particulate is not appropriate for risk assessment purposes, OEHHA persists with using rat data for their unit risk calculations. Although we do not endorse the use of rat data in such a calculation, we have noted some problems and errors in Chapter 7 of OEHHA, Part B (1997). Specifically,

- p. 7-1: Particle concentration is selected because it is a “*commonly used measure.*” This is inadequate justification. OEHHA needs to carefully discuss the implications of their choice of dose metric. That is, if lung cancer risk in humans cannot be based lung overload mechanisms, then (OEHHA would say) adsorbed organic content is more relevant than the mass of diesel particulate. This choice would likely require that all of the organic material were bioavailable, which is highly unlikely. Furthermore, if the quantity of adsorbed organics is the relevant dose parameter, then the fuel type and operating conditions become very important and cannot be dismissed by the Office. For example, the locomotive fuel and operation of diesel train engines characteristic of worker exposure in the Garshick *et al.* studies are not equivalent to the fuel type and diesel exposure conditions for the California population today.
- p. 7-3: For the animal studies, “*the lung burden dose measure was assumed on theoretical grounds to be a better predictor of tumorigenicity.*” Yet, “*lung burden was not used to calculate risk estimates from human study data*” because exposures were not great enough. In OEHHA's 1994 draft, lung burden in humans was described as a more relevant exposure metric, and the reason for the change appears to be ad hoc.
- p. 7-3: It is stated that “*lung burden estimates were derived from the model of Yu and associates (1991)*”, yet on Table 7-1, pp. 7-30, Hattis and Silver (1992) are given as the source of the lung burden model.
- p. 7-4: The same paragraph that says “*rat data are consistent with ... risk estimates of 16 to 160 cases per million*” also states that “*risk estimates ... differed by less than five-fold.*” Is this discrepancy fall within OEHHA's rubric of “*relatively consistent*”?
- p. 7-5: What is the effect of “*censoring of such observations due to any deaths in which lung tumors were not detected*”?
- p. 7-5: Are computations that “*gave the value zero for the latency period*” consistent with biology?

- p. 7-7: It is stated that the model-derived q_1 refers to 35 hr/wk of rat exposure. Hence, an additional correction is applied to derive a q_1 for continuous human lifetime exposure. However, on the top of p. 7-5 it is made clear that the rat doses that were entered into the model were “lifetime- $\mu\text{g}/\text{m}^3$.” Thus, it would seem that the intermittent rat exposure was doubly (and redundantly) corrected.
- p. 7-8: Perhaps because of OEHHA's (p. 7-7) redundant correction, Table 7.3 and Table 7.7 report different values for what would seem to be the same result. On Table 7.3, the “95% UCL for human unit cancer risk, based on concentration,” and developed from the Mauderly study is 9×10^{-5} . Whereas on Table 7.7, the “Human 95% UCL for unit risk for diesel exhaust”, based on concentration, and predicted from the Mauderly rat data is 28×10^{-5} . This three-fold difference does not give confidence about the precision of OEHHA's modeling procedures.
- p. 7-12: The calculation comparing lung burdens at the bottom of the p. is incorrect. On the top of p. 7-13, it is stated that the ratio of human lung burden per alveolar surface area, at ambient diesel concentrations, is only 500 times less than the rat lung burden per alveolar surface area for the test chamber atmospheres. Yet, the rat lung burden is $6,220 \mu\text{g}/0.4 \text{ m}^2 = 15,600 \mu\text{g}/\text{m}^2$, and the human lung burden is $4.2 \mu\text{g}/135 \text{ m}^2 = 0.031 \mu\text{g}/\text{m}^2$. **Thus, the difference is a factor of 500,000, not 500.** Again, this loss of a factor of 1,000 does not give confidence in the modeling procedures.

It is important to stress that correcting these errors will not compensate for the inappropriate use of the rat data to begin with.

5.2 Use of Lung Cancer Risk in Diesel-Exposed Rats to Predict Lung Cancer Deaths in Carbon Black Workers

The production of lung tumors in rats after chronic particle inhalation is not predictive of human risk, particularly in the case of workers in carbon-black manufacturing, who do not exhibit an excess lung cancer risk (Valberg and Watson, 1996). OEHHA discounts this observation by referring to “a new Canadian study showing carcinogenicity in humans exposed to carbon black.” (p. 7-26, Part B, OEHHA). However, the referred-to publication (Parent *et al.*, 1996) did not report on workers in carbon black manufacturing; the study population had only presumptive exposure to carbon black, and in fact, experienced exposures to many other substances. OEHHA elaborates on this statement in Appendix C, and attempts to question this lack of concordance between rats and humans by citing Parent's case-control study (1996). In addition, the Office presents alternative assumptions for the analysis by Valberg and Watson. OEHHA's discussions in Appendix C are flawed on two counts:

- The cited study does not show what OEHHA attributes to it.
- OEHHA's criticisms of the lack of concordance between rat and human responses to carbon black are inaccurate.

5.2.1 Shortcomings of the Parent *et al.* (1996) Study

The Parent *et al.*, (1996) data were derived from a Canadian population-based epidemiologic study that evaluated various health indices and occupations, some of which had presumptive exposure to carbon black (Siemiatycki *et al.*, 1991). Parent *et al.* (1996) conducted additional analyses of the lung-cancer cases identified in Siemiatycki's population-based study. Because of the attention drawn to this study by OEHHA, it is important to clarify the degree to which this study can be relied upon for carbon-black, lung-cancer risk assessment.

In Siemiatycki's data base (1991), patients were interviewed to obtain information on work history. A team of hygienists and chemists then assigned possible occupational exposures to the various job categories. Exposure to carbon black was judged to occur only in user industries, such as the painting, printing, and rubber industries (the population did not include any workers in carbon black manufacturing). After adjusting for various factors, the investigators calculated a total of eight odds ratios (ORs) as follows: two target populations ("*all workers*", "*French-Canadians only*") were compared to two control groups ("*general population*", "*cancer controls*") over two exposure categories ("*any*", "*substantial*"). For presumptive carbon-black exposure, two of the eight ORs were reported to be statistically significant at the $p = 0.10$ level. When compared to cancer controls, "*all workers*" having "*any*" or "*substantial*" exposure history to carbon black experienced an increased lung-cancer risk; all other ORs were not significant.

The major shortcoming of Siemiatycki's data base is exposure assessment. First, actual exposure to airborne carbon black was not documented; exposure was only inferred from patient interview and the assumption of exposure from job descriptions. Second, those workers with an increased risk of lung cancer were primarily in the **printing** and **publishing** industries, which involve exposure to known or suspect organic carcinogens but with no demonstrated exposure to pure airborne carbon black. For example, Table 1 from Siemiatycki's monograph (1991) notes that workers assigned to exposure to

carbon black were also exposed to numerous other compounds, several of which were also associated with an increased risk of lung cancer (see Table 7). However, the authors did not control for confounding due to simultaneous occupational exposures.

In the Parent *et al.* (1996) analyses, lung-cancer patients were matched with population controls and cancer controls. Again, presumed exposure to carbon black was assigned by a team of chemists and hygienists. The authors constructed a cumulative exposure index using variables for concentration, frequency, confidence of exposure, and duration of job. They categorized cumulative exposure as either “*unexposed*”, “*lower*”, or “*higher*”, depending on the numerical value of the index. Of the entire study population, only 5.3% were assigned some exposure to carbon black. The majority of such exposure occurred in painters and paperhangers (26%), printing press operators (12%), and motor vehicle mechanics and repairers (8%). Although carbon black was considered present in these occupations, the authors did not distinguish between inhalation, accidental ingestion, or dermal contact. In addition, the chemical and physical form of the carbon black was not characterized. There were substantial differences, including smoking status, between the lung-cancer cases and the two control groups. The authors adjusted for some of these factors in their analyses. The authors reported that “*some increase in risk for all lung cancers was apparent*”. However, Table V from their paper shows that for seven out of eight ORs, the lower 95% CI were less than 1.0, indicating non-significance of any elevated OR's. The authors presented no statistical tests to determine significance levels. Also, because there was a dramatic difference in smoking status between the lung-cancer patients and the two control groups, it is unclear why the crude and adjusted ORs are so similar; they should have been very different.

In summary, Siemiatycki's monograph (1991) reported that he had found a significant increase in lung-cancer ORs for workers with a presumed exposure to carbon black, but no specific carbon-black exposure data were available, no dose-response could be demonstrated, and the workers was also exposed to other potential lung carcinogens, which were not controlled for in the analyses. Furthermore, of eight different ORs, only two were statistically significant at $p = 0.10$. Parent's analyses (1996) also failed to obtain adequate exposure information, and significance was not supported by proper statistical tests. It is not possible to conclude that the results from this study showed any an association between airborne carbon black exposure and lung-cancer risk.

Thus, it is clear that the probative value of the Parent *et al.* (1996) work as a comment on risk of carbon black exposure is poor at best. In fact, the authors acknowledged that exposure to carbon black was probably minor compared to exposures to other substances.

5.2.2 Inaccuracies in OEHHA's criticisms of the Valberg and Watson (1996) analysis

In Appendix C, OEHHA undertakes a complex series of analyses based on alternative assumptions. While some of these different assumptions represent acceptable fine tuning, OEHHA has lost sight of two simple points. One, OEHHA's complex analysis obscures the basic definition of unit risk. The definition of the unit risk value is that, when it is multiplied by the lifetime average concentration, the result is the lifetime cancer risk. Hence the calculations presented in the Valberg and Watson (1996) paper are correct, notwithstanding OEHHA's efforts to minimize the lack of concordance between rat predictions and human experience in the case of carbon black. It should be emphasized that the same lack of concordance exists in the case of coal dust, where rats have been shown to develop lung tumors after coal dust inhalation, yet the extensive record of coal miners with heavy lung burdens of retained coal dust does not reveal excess lung cancer risk.

Two, OEHHA in its own document, claims to detect an excess lung cancer risk in the Garshick *et al.* (1988) cohort data for railroad workers. The average lifetime concentration of diesel exhaust is given by OEHHA as $64 \mu\text{g}/\text{m}^3$ (p. 7-21, Part B, OEHHA). If the rat bioassay were valid, and because it predicts equivalent carcinogenicity for diesel exhaust and carbon black, the "cancer signal" in carbon black manufacturing workers should be in proportion to their lifetime exposure. Because the average lifetime concentration of carbon black for the historical cohorts studied was approximately $410 \mu\text{g}/\text{m}^3$ (Valberg and Watson, 1996), the hypothetical lung cancer risks for carbon black workers should be **6.4× larger** than for Garshick *et al.*'s railroad workers. How could such an excess have been missed? The answer is that the particle-inhalation bioassay in rats is not applicable to predicting human cancer risk.

As pointed out in Section 5.1, worker lifetime exposure to significantly elevated levels of carbonaceous particles (carbon black, coal dust) have not been associated with increased lung cancer risk. Carbon black particles are very similar in size and composition to diesel exhaust, and even though coal dust is larger in size, lifetime inhalation produces significant lung retention of the fine particle fraction of coal dust. The fact that human lung reactions to these two particles are so dissimilar to the rat lung response severely undermines the utility of the rat for diesel exhaust risk assessment.

5.3 Conclusion

The lung tumor data from rats chronically exposed to high levels of diesel exhaust should not be used for estimating lung cancer unit risk. For insoluble particles, the lung tumor response is rat specific and not particle specific. Other rodents exposed to insoluble particles do not develop lung tumors, and epidemiologic studies of workers exposed to insoluble particles do not report an excess of lung cancer.

6 Overall Conclusions

CalEPA has misrepresented the current understanding of the carcinogenic potential of diesel-engine exhaust. The Office is unwilling to accept the limitations of the scientific knowledge and persists in the use of epidemiologic data and rat studies for quantitative risk assessment. Specifically, the Office ignores the significance of the following:

- The epidemiologic studies were not designed to be used for risk assessment purposes. The existence of any dose-response remains problematic. We do not have adequate information on exposure and smoking in worker populations exposed to diesel-engine exhaust. With such low relative risks, it is essential that exposure data be available and that confounding variables be controlled.
- A mechanism of action for the proposed carcinogenicity of diesel exhaust in humans has not been identified. In rats, it appears the diesel exhaust-induced tumorigenesis is mediated by non-genotoxic mechanisms that exhibit a threshold. The evidence for genotoxic mechanisms for diesel exhaust is speculative and cannot be used to justify linear-dose models.
- The rat is an outlier and exhibits a non-specific response to concentrations of inhaled particulate that lead to lung overload. This finding has been shown repeatedly and has led several scientific advisory groups to discount the rat inhalation bioassay for assessing human cancer risk.

The Office is pursuing a course of action, by its recommendation of diesel exhaust as a TAC, that is not supported by the current state of knowledge. The scientific community is not unanimous in its understanding of diesel exhaust and readily acknowledges the uncertainty involved. In spite of the uncertainty, the HEI (1995) concluded, that, even if the rat data were applicable to humans:

“The average levels of diesel found in most occupational settings, which are below 100 $\mu\text{g}/\text{m}^3$, would not likely be a cancer hazard for these workers, nor would ambient levels (1 to 10 $\mu\text{g}/\text{m}^3$) present a cancer risk for the general population.” (p. 1)

The HEI (1995) also concluded,

“...the available epidemiologic and animal data are insufficient to ... be used in quantitative risk assessments.” (p. 2).

This viewpoint is supported by the investigators who have generated the data upon which OEHHA bases their risk assessment calculations. Mauderly, the lead investigator for the rat studies, has stated that the rat inhalation bioassay for particulate should not be used for quantitative risk assessment (CASAC, 1995 see also Mauderly, 1994). Garshick (1995) has also indicated that his work was not designed and not intended for use in risk assessment exercises. However, OEHHA has chosen to ignore such statements and by using Mauderly's rat study and the Garshick *et al.* epidemiologic studies, OEHHA conducted several risk assessments that led the Office to conclude (Executive Summary, p. 14),

“At recent and current ambient concentrations, diesel exhaust produces a significant increase in the likelihood of cancer. Therefore, diesel exhaust clearly meets the legal definition of a TAC...”

OEHHA has misused the scientific literature and is burdening the California population with the misapprehension that ambient diesel exhaust poses a significant risk to their health and welfare.

References

- Brandt, A.M. 1990. The cigarette, risk, and American culture. *Daedalus*. 119(4): 155-176. Fall.
- Brooks, A.L., R. K. Wolff, R.E. Royer, C.R. Clark, A. Sanchez, and R.O. McClellan. 1981. Deposition and biological availability of diesel particles and their associated mutagenic chemicals. *Environ Intl* 5:263-267.
- Chen, J.L., and Fayerweather, W.E. (1988). Epidemiologic study of workers exposed to titanium dioxide. *J Occup Med* 30, 937-942.
- Clark, C.R. and C.L. Vigil. 1980. Influence of rat lung and liver homogenates on the mutagenicity of diesel exhaust particulate extract. *Toxicol Appl Pharmacol* 56:110-115.
- Clean Air Scientific Advisory Committee (CASAC). 1995. Letter from George T. Wolff, Chair of the Clean Air Scientific Advisory Committee to the Honorable Carol M. Browner, Administrator of the U.S. Environmental Protection Agency, Dated August 3, 1995.
- Cohen, A.J., and M.W.P Higgins. 1995. Health effects of diesel exhaust: Epidemiology. In: Health Effects Institute. Diesel Exhaust: *A Critical Analysis of Emissions, Exposure, and Health Effects: A Special Report of the Institute's Diesel Working Group*. April.
- Driscoll, K.E. 1996. Role of inflammation in the development of rat lung tumors in response to chronic particle exposure. *Inhala Toxicol* 8(suppl):139-153.
- Driscoll, K.E., J.M. Carter, B.W. Howard, D.G. Hassenbein, W. Pepelko, R.B. Baggs, and G. Oberdorster. 1996. Pulmonary inflammation, chemokine, and mutagenic responses in rats after subchronic inhalation of carbon black. *Toxicol Appl Pharm* 136:372-380.
- Driscoll, K.E., L.C. Deyo, J.M. Carter, B.W. Howard, D.G. Hassenbein, and T.A. Bertram. 1997. Effects of particle exposure and particle-elicited inflammatory cells on mutation in rat alveolar epithelial cells. *Carcinogen* 18:101-108.
- Garschick, E. 1995. Letter to Mr. Randall Bond, U.S. EPA, Scientific Advisory Board. May 30, 1995.
- Garshick *et al.*, E., M.B. Schenker, A. Munoz, M. Segal, T.J. Smith, S.R. Woskie, K.S. Hammond, and F.E. Speizer. 1987. A case-control study of lung cancer and diesel exhaust exposure in railroad workers. *Am Rev Respir Dis* 135:1242-1248.
- Garshick *et al.*, E., M.B. Schenker, A. Munoz, M. Segal, T.J. Smith, S.R. Woskie, K.S. Hammond, and F.E. Speizer. 1988. A retrospective cohort study of lung cancer and diesel exhaust exposure in railroad workers. *Am Rev Respir Dis* 137:820-825.
- Gaylor, D.W., and Q. Zheng. 1996. Risk assessment of nongenotoxic carcinogens based upon cell proliferation/death rates in rodents. *Risk Anal* 16:221-225.

Health Effects Institute (HEI). 1995. *Diesel Exhaust: Critical Analysis of Emissions, Exposure, and Health Effects*. Cambridge, MA: Health Effects Institute.

Hemminki, K., J. Soderling, P. Ericson, H.E. Norbeck, and D. Segerback. 1994. DNA adducts among personnel servicing and loading diesel vehicles. *Carcinogen* 15:767-769.

Heinrich, U., R. Fuhst, S. Rittinghausen, O. Creutzenberg, B. Bellmann, W. Koch, and K. Levsen. 1995. Chronic inhalation exposure of Wistar rats, and two different strain of mice to diesel engine exhaust, carbon black and titanium dioxide. *Inhal Toxicol* 7:533-556.

Henderson, R.F., J.A. Pickrell, R.K. Jones, J.D. Sun, J.M. Benson, J.L. Mauderly, and R.O. McClellan. 1988. Response of rodents to inhaled diluted diesel exhaust: Biochemical and cytological changes in bronchoalveolar lavage fluid and in lung tissue. *Fund Appl Toxicol* 11:546-567.

Hou, S., B. Lambert, and K. Hemminki. 1995. Relationship between hprt mutant frequency, aromatic DNA adducts and genotypes for GSTM1 and NAT2 in bus maintenance workers. *Carcinogen* 16:1913-1917.

International Agency for Research on Cancer (IARC). 1997. *IARC Monographs on the Evaluation of Carcinogenic Risk to Humans: Silica, Some Silicates, Coal Dust and para-Aramid Fibrils (Vol. 68)*. World Health Organization, Lyon, France.

Kanoh, T., M. Fukuda, H. Onozuka, T. Kinouchi, and Y. Ohnishi. 1993. Urinary 1-hydroxypyrene as a marker of exposure to polycyclic aromatic hydrocarbons in environment. *Environ Res* 62:230-241.

Keane, M.J., S-G. Xing, J.C. Harrison, T. Ong, and W.E. Wallace. 1991. Genotoxicity of diesel-exhaust particles dispersed in simulated pulmonary surfactant. *Mut Res* 260:233-238.

King, L.C., M.J. Kohan, A.C. Austin, L.D. Claxton, and J.L. Huising. 1981. Evaluation of the release of mutagens from diesel particles in the presence of physiological fluids. *Environ Mutagen* 3:109-121.

King, L.C., K. Loud, S.B., Tejada, M.J. Kohan, and J. Lewtas. 1983. Evaluation of the release of mutagens and 1-nitropyrene from diesel particles in the presence of lung macrophages in culture. *Environ Mutagen* 5:577-588.

Mauderly, J.L. 1994. Contribution of inhalation bioassays to the assessment of human health risks from solid airborne particles. In *Toxic and Carcinogenic Effects of Solid Particles in the Respiratory Tract* (U. Mohr, D.L. Dungworth, J.L. Mauderly, and G. Oberdorster, Eds.), pp. 355-365. ILSI Press, Washington, DC.

Mauderly, J.L., and R.J. McCunney (Eds.). 1996. *Particle Overload in the Rat Lung and Lung Cancer: Implications for Human Risk Assessment*. Taylor and Francis, Washington, D.C.

Mauderly, J.L., M.B. Snipes, E.B. Barr, S.A. Belinsky, J.A. Bond, A.L. Brooks, I-Y. Chang, Y.S. Cheng, N.A. Gillett, W.C. Griffith, R.F. Henderson, C.E. Mitchell, K.J. Nikula, and D.G. Thomassen. 1994. Pulmonary toxicity of inhaled diesel exhaust and carbon black in chronically exposed rats. Health Effects Research Report No. 68. Health Effects Institute, Cambridge, MA.

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

McClellan, R.O., R.G. Cuddihy, W.C. Griffith, and J.L. Mauderly. 1989. Integrating diverse data sets to assess the risks of airborne pollutants. In: *Assessment of Inhalation Hazards* (Bates, D.V., D.L. Dungworth, P.N. Lee, R.O. McClellan, F.J.C. Roe, Eds.). Springer-Verlag, ILSE Monographs: 1-22.

Muscat, J.E., and E.L. Wynder. 1995. Diesel engine exhaust and lung cancer: An unproven association. *Environmental Health Perspectives*. 103(9): 812-818. September.

National Institute for Occupational Safety and Health. 1986. Coal workers' pneumoconiosis and exposure to other carbonaceous dusts. In *Occupational Respiratory Diseases* (J.A. Merchant, B.A. Boehlecke, and G. Taylor, Eds.). US Department of Health and Human Services Publication, Center for Disease Control, US Government Printing Office, Washington, DC.

Nielsen, P.S., A. Andreassen, P.B. Farmer, S. Ovrebo, and H. Autrup. 1996. Biomonitoring of diesel exhaust-exposed workers: DNA and hemoglobin adducts and urinary 1-hydroxypyrene as markers of exposure. *Tox Lett* 86:27-37.

Office of Environmental Health Hazard Assessment (OEHHA). 1994. *Health Risk Assessment for Diesel Exhaust (Preliminary Draft)*. California Environmental Protection Agency. June.

Office of Environmental Health Hazard Assessment (OEHHA). 1997. *Health Risk Assessment for Diesel Exhaust (Public and Scientific Review Panel Review Draft)*. California Environmental Protection Agency. March.

Parent, M.-E., J. Siemiatycki, and G. Renaud. 1996. Case-control study of exposure to carbon black in the occupational setting and risk of lung cancer. *Am J Indust Med* 30:285-292.

Presidential/Congressional Commission on Risk Assessment and Risk Management (CCRARM). 1997. *Risk Assessment and Risk Management in Regulatory Decision-Making. Volume 2, p. 65 (pp. 1-213)*

Scheepers, P.T.J., H.J.T.M. Thuis, M.H.J. Martins, and R.P. Bos. 1994. Assessment of occupational exposure to diesel exhaust. The use of an immunoassay for the determination of urinary metabolites of nitroarenes and polycyclic aromatic hydrocarbons. *Tox Lett* 72:191-198.

Schenker, M.B. N.Y. Kado, S.K. Hammond, S.J. Samuels, S.R. Woskie, and T.J. Smith. 1992. Urinary mutagenic activity in workers exposed to diesel exhaust. *Environ Res* 57:133-148.

Siak, J.S., T.L. Chan, and P.S. Lee. 1981. Diesel particulate extracts in bacterial test systems. *Environ Intl* 5:243-248.

Siemiatycki, J., (Ed.). 1991. *Risk Factors for Cancer in the Workplace*. CRC Press, Boca Raton, FL.

Speizer, F.E. 1986. Overview of the risk of respiratory cancer from airborne contaminants. *Environmental Health Perspectives*. 70: 9-15.

Stober, W. and U.R. Abel. 1996. Lung cancer due to diesel soot particles in ambient air? A critical appraisal of epidemiological studies addressing this question. *International Archives of Occupational Environmental Health*. Supplement to volume 68: S-3 - S-61.

Stokinger, H.E. 1984. A review of world literature finds iron oxides noncarcinogenic. *Am Ind Hyg Assoc J* 45:127-133.

United States Environmental Protection Agency (U.S. EPA). 1988. Toxic chemical release reporting; community right-to-know; titanium dioxide. *Federal Register* 53:23108-23111.

United States Environmental Protection Agency (U.S. EPA). 1994. *Health Assessment Document for Diesel Emissions (External Review Draft)*. Volume I. EPA 600/8-90/05/8a.

Valberg, P.A., and A.Y. Watson. 1996. Lung cancer rates in carbon-black workers are discordant with predictions from rat bioassay data. *Reg Toxicol Pharm* 24:155-170.

Wallace W.E., M.J. Keane, C.A. Hill, J. Xu, and T. Ong. 1987. Mutagenicity of diesel exhaust particles and oil shale particles dispersed in lecithin surfactant. *J Toxicol Environ Health* 21:163-171.

Watson, A.Y., and P.A. Valberg. 1996. Particle-induced lung tumors in rats: Evidence for species specificity in mechanisms. *Inhal Toxicol* 8(suppl):227-257.

Wergeland, E., Anderson, A., and A. Baerheim. 1990. Morbidity and mortality in talc-exposed workers. *Am. J. Ind. Med.* 17, 505-513.

World Health Organization. 1996. *Diesel Fuel and Exhaust Emissions (Environmental Health Criteria 171)*. International Programme on Chemical Safety.

Woskie, S.R., T.J. Smith, S.K. Hammond, M.B. Schenker, E. Garshick *et al.*, and F.E. Speizer. 1988a. Estimation of the diesel exhaust exposures of railroad workers: I. Current exposures. *American J of Ind Med*, 13: 381-394

Woskie, S.R., T.J. Smith, S.K. Hammond, M.B. Schenker, E. Garshick *et al.*, and F.E. Speizer. 1988b. Estimation of the diesel exhaust exposures of railroad workers: II. National and historical exposures. *American J of Ind Med*, 13: 395-404.

Figures

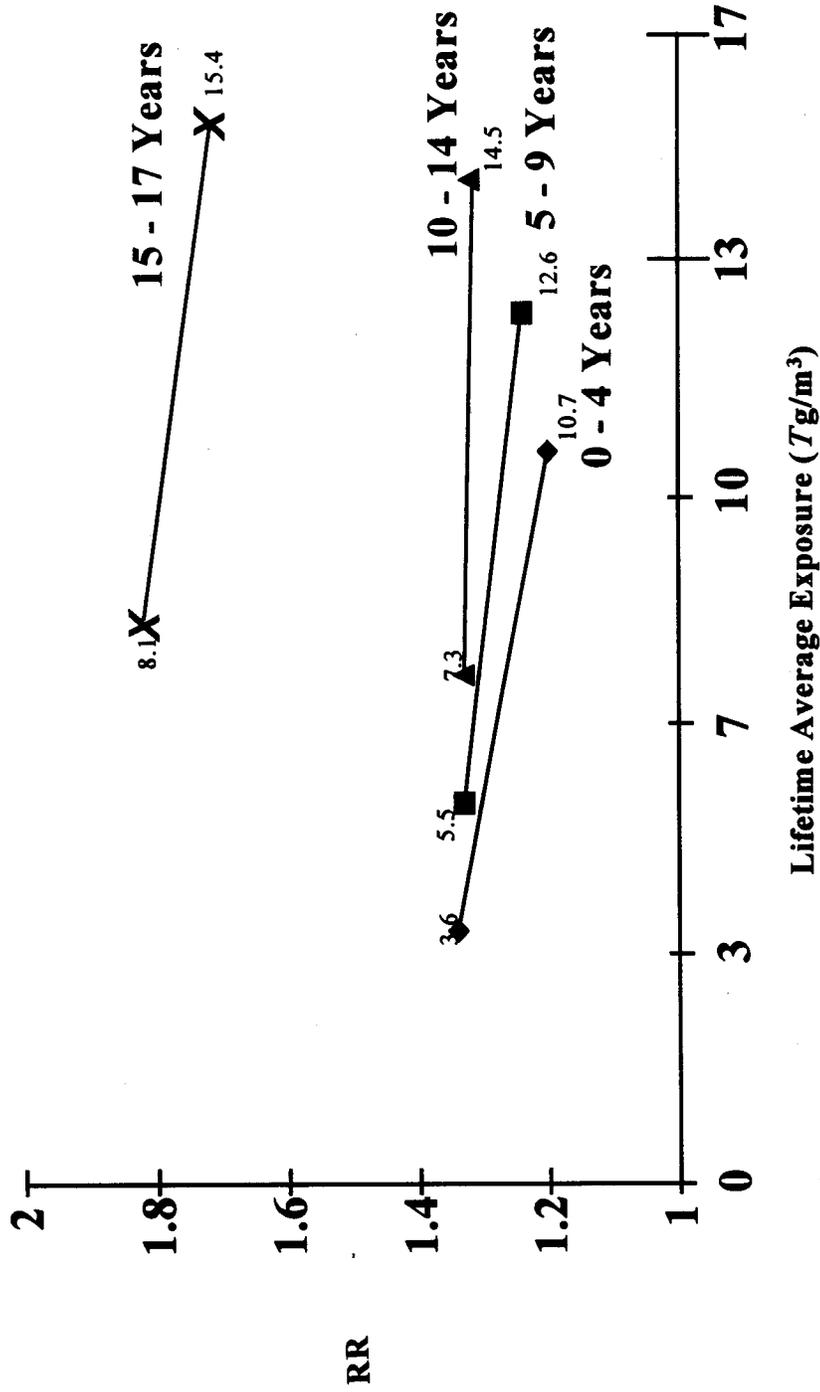


Figure 2.1

Diesel exhaust exposure versus relative risk shows no dose-response. Point at the left end of each line represents exposed workers, excluding shopworkers. Point at the right end of each line represents all exposed workers.

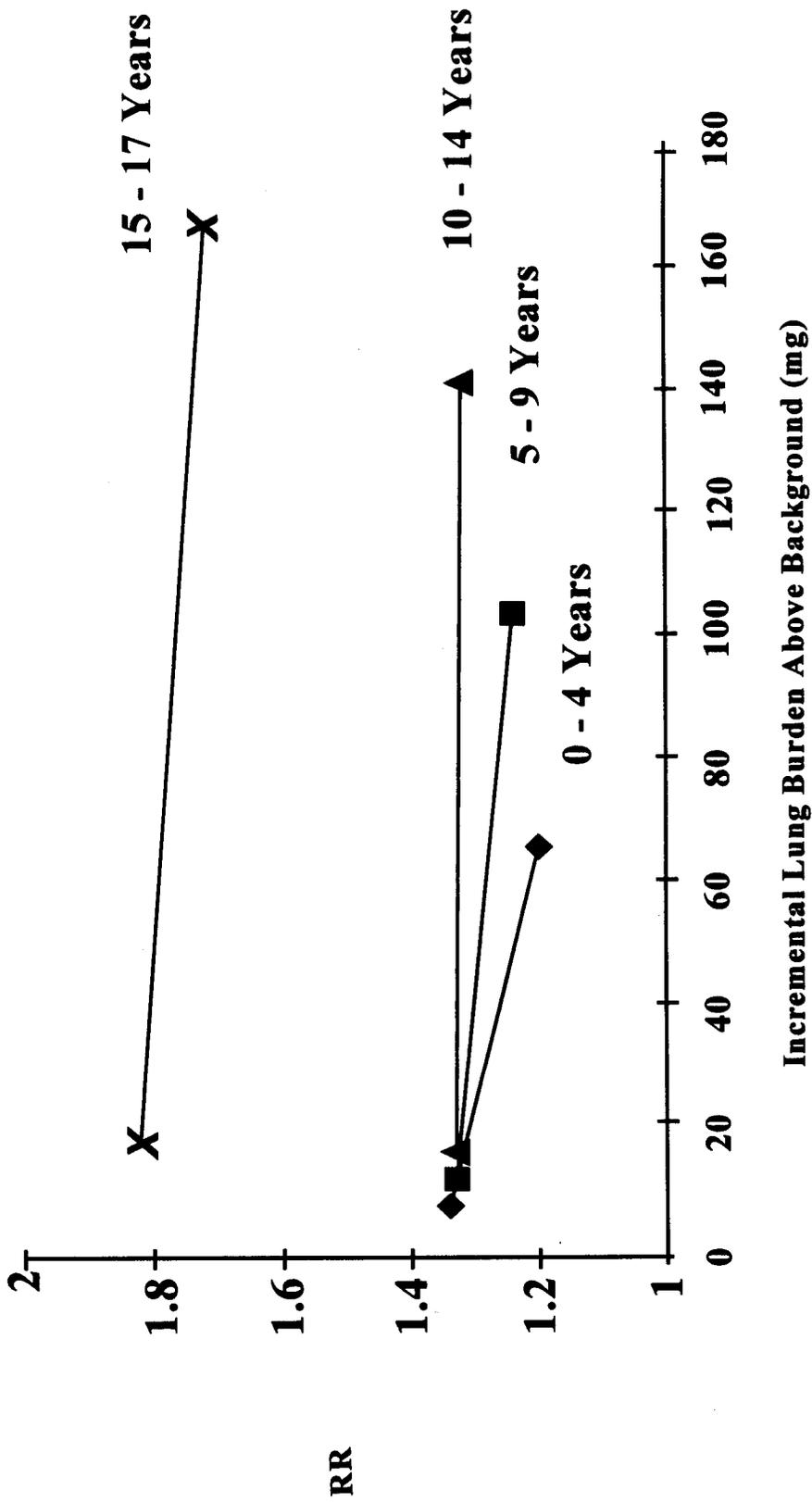


Figure 2.2

Diesel exhaust lung burden versus relative risk shows no dos-response. Point at the left end of each line represents exposed workers, excluding shopworkers. Point at the right end of each line represents all exposed workers.

**COMMENTS ON OEHHA'S 1997 DRAFT RISK
ASSESSMENT FOR DIESEL EXHAUST**

August 20, 1997

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EXECUTIVE SUMMARY

OEHHA's 1997 draft risk assessment for diesel exhaust (DE) retains essential features of its 1994 draft risk assessment. OEHHA received many technical criticisms of its 1994 risk assessment in public comments, e.g., as reflected in the current draft's discussion of "uncertainties" about its methods and conclusions (especially Sections 7.2.8 and 7.3.3). A key question is whether the technical objections that have been raised threaten the validity of OEHHA's main conclusions, or whether they only point out ways to further improve an analysis that is basically sound. For example, OEHHA now acknowledges the following sources of "uncertainty" in their analysis:

- Use of approximate instead of exact model formulas;
- Ignored exposure uncertainties and measurement errors (p. 7-22);
- Treatment of assumed models as if they were known to be true;
- Restriction of the set of models considered to those that are low-dose-linear (p. 7-20);
- Ignored heterogeneity in individual exposures and response parameters (p. 7-22).

But are they more than just uncertainties – are they outright mistakes that invalidate OEHHA's main conclusions? How might one tell? This document examines each of OEHHA's main conclusions, and the arguments supporting them, from the perspective of how OEHHA has addressed or dismissed the above-noted uncertainties in their analysis of animal data, epidemiological data, meta-analysis, and causal interpretation. We find that most of their key conclusions about risk are not implied by (or even always consistent with) available data, but that instead that they arise primarily from modeling assumptions and practices corresponding to what OEHHA acknowledges as areas of "uncertainty". It appears that the key conclusions that OEHHA has drawn are assumption-driven rather than data-driven. The facts and data are, on their own merits, more consistent with the conclusion that DE creates no significant excess risk in humans at low exposure levels than with OEHHA's assumption-based conclusion that DE poses a significant risk (approximately proportional to cumulative exposure) even at low doses.

A point that critics of OEHHA's DE risk assessment have so far failed to persuade OEHHA Staff to accept is that many of the identified areas of uncertainty could be resolved relatively easily using more appropriate statistical methods. Such methods appear throughout the modern statistical and

biostatistical literatures and can be implemented easily using widely available statistical software. Technically, models that represent uncertainty in exposure estimates, allow for interindividual heterogeneity, and are flexible enough to admit the possibility of low-dose nonlinearity would appear to be unambiguously more appropriate for modeling DE risk data than models that don't. However, OEHHA has chosen not to use such methods, instead opining that the techniques they have used, despite their recognized errors and limitations, produce answers that might not be very inaccurate and that OEHHA considers "adequate" (C-OEHHA, 167, 168, 170). OEHHA's criteria for model adequacy are not stated. The basis for preferring simpler, less correct models to more complex, more accurate models is unclear, given the capabilities of modern statistics software. Tables 3, 4, and 6 offer suggestions for applying more accurate statistical methods to correct some of the main errors/limitations in OEHHA's modeling approach.

The main purpose of this document is to see what new can be added to the discussion of human risks from DE exposure to simplify and clarify the main policy-relevant issues. The following new points go well beyond technical niceties. They address the central logic of OEHHA's analysis and conclusions.

1. ***OEHHA's analysis of animal data is seriously flawed by unjustified aggregation of rat tumor data across sexes.*** This is statistically invalid and creates a serious error of aggregation. When the Mauderly *et al.* tumor data for male and female rats are analyzed separately, both contain apparent response thresholds, contradicting OEHHA's findings based on the pooled data. The threshold hypothesis is better supported by the data than OEHHA's assumption of low-dose linearity. Correctly analyzed (i.e., without pooling tumors across sexes), the Mauderly *et al.* rat data do not support OEHHA's conclusions about low-dose risk. This finding is not new. Mauderly *et al.* originally stated that their data tends to support the hypothesis of a threshold for response. What is new is OEHHA's use of aggregation to obscure the threshold patterns in the data and contradict the findings of the original researchers.
2. ***OEHHA's reanalysis of the Garshick *et al.* data is flawed by failure to correct for the confounding effects of factors such as year of birth and age at death (which are positively associated with both lung tumor rate and average DE exposure.)*** When the effects of such confounding are removed, DE concentration is negatively associated with lung cancer rate. Thus, the Garshick *et al.* data do not support OEHHA's conclusions of a positive statistical association (nor of a causal relation) between DE exposure and human lung cancer. This is consistent with Garshick's own finding and reanalysis of his own data. As described by Cohen and Higgins (1995), "Recently, Garshick reanalyzed these data and found that when the effect of age was allowed to vary within birth cohorts, the apparent upward trend in the

relative risk for cumulative exposure disappeared". (It is also consistent with independent work by Dr. Kenny Crump, who has repeatedly pointed out to OEHHA, using different analyses, that the *Garshick et al.* data do not support OEHHA's interpretation of a significant positive association between DE exposure and lung cancer risk.) The reanalysis of the *Garshick et al.* cohort data with correction for confounding has been peer-reviewed and will be published in *Risk Analysis* later this year (Cox, 1997). Its main methods and findings were shared with OEHHA in 1995 and 1996.

3. *OEHHA's new meta-analysis is flawed by failure to correctly calculate p-values to correct for false positives due to multiple comparisons and multiple hypothesis testing. This problem also occurs in many of the individual studies cited by OEHHA, including the studies of Garshick et al. The result is that a pattern of consistently elevated relative risks is expected, whether or not DE exposure has a positive effect on lung cancer risk. Since this is the pattern that has been observed, OEHHA's meta-analysis offers no evidence either for or against the hypothesis that DE exposure has a genuine causal association with human lung cancer risk (as opposed to merely a statistical association due to improperly controlled false positives).*
4. *OEHHA's causal interpretation of the relation between DE exposure and human lung cancer (Section 6.2.4) is unsupported by any formal statistical tests for causation. The reported associations are expected based solely on the statistical methods used, even if DE exposure has no effect on lung cancer. Thus, OEHHA's meta-analysis does not support the conclusion that DE exposure contributes to human lung cancer risk.*

In summary, none of the three data sources that OEHHA uses – rat, *Garshick et al.*, and meta-analysis – is sufficiently robust to allow a conclusion that DE creates low-dose cancer risks in humans. Nor has OEHHA performed statistical tests of this hypothesis. Of course, they may simply assume that DE exposure causes human cancer risks. But then it should be made explicit to decision-makers that this conclusion rests solely on OEHHA's opinions and modeling assumptions and is not dictated either by correct analysis or by facts and data. The following sections develop these points more fully.

A. ANALYSIS OF RAT DATA

Section 7.2 of OEHHA's draft risk assessment applies a traditional multistage model and a "simplified Moolgavkar model" to the 1987 data of Mauderly *et al.* and concludes (Table 7.7, p. 7-38) that the 95% upper confidence limits for extrapolated unit risks in humans should fall in the range from 0.5×10^{-4} to 2.8×10^{-4} per microgram-per-cubic meter of DE concentration in inhaled air, depending on what assumptions are made about the appropriate dose metric. OEHHA

interprets this outcome as reinforcing their findings based on epidemiological data, and uses it to bolster their conclusion that relatively low levels of DE may create a substantial risk of lung cancer in exposed human populations.

Since 1994, many commenters have questioned OEHHA's use and interpretation of these data. Table 1 lists representative technical comments and summarizes OEHHA's responses. The following additional points are intended to simplify the discussion by noting that the experimental rat data do not address the low-dose issues of practical interest, that they do not support (and are not required for) OEHHA's conclusions about low-dose risks, and that the modeling issues about them are therefore irrelevant and can be disregarded. OEHHA's conclusions must stand or fall based on their epidemiological data analysis.

1. Available rat data do not address low-dose risks and provide no evidence of increased risk at low doses. We believe that, as a matter of logic, the Mauderly *et al.* data cannot be used to draw sound inferences about low-dose risks for DE. Our reasoning is as follows.

- **Premise 1: The Mauderly *et al.* data only show significantly elevated risks at the two highest dose levels.** Table 2 recapitulates the original Mauderly *et al.* data, including squamous cysts. (As noted by OEHHA, inclusion or exclusion of the cysts makes little difference to the conclusions.)

Note that OEHHA's Table 7.1 aggregates these data across the two sexes. This masks the fact that the lowest non-zero dose level is associated with a *decrease* in observed tumors among male rats, rather than with an increase as predicted by both of OEHHA's models (Weibull multistage and simplified Moolgavkar).

Among female rats, a ten-fold increase in concentration from 0.35 to 3.5 is matched by only a two-fold increase in risk, but a further doubling of concentration is then matched by a quadrupling of observed tumor risk. If the dose-response relation has a conventional sigmoid shape, then this data pattern suggests that at low doses, there is substantial background risk of lung cancer among female rats, with only sampling variability observed at the two or three lowest concentrations. A significant positive (upward-curving) effect of concentration on lung cancer takes place only above 0.35, making it plausible that, at the two lower concentrations, there is no effect of dose on tumor rate. Thus, these data do not support OEHHA's claim that tumor risks are elevated at the lowest dose level (implied by both of the two models, Weibull multistage and simplified Moolgavkar that OEHHA has examined), and that no evidence of a threshold can be found.

In summary, OEHHA has aggregated two dose-response patterns, one for each sex, each of which is more consistent with the hypothesis of a response threshold than with the hypothesis of low-dose linearity, to obtain a composite

TABLE 1: Past Criticisms of OEHHA's Animal DE Risk Assessment

CRITICISM	OEHHA's RESPONSE	REJOINDER/RECOMMENDATION
<p>1. The draft risk assessment ignores scientifically relevant information about the mechanism of DE cancer induction in rats, which does not apply to humans at realistic exposure levels. (C-OEHHA-146, Comment 9)</p>	<p>DE particles and associated organics are genotoxic and potentially might contribute to a low-dose cancer risk.</p> <p>The epidemiological studies discussed in the TSD provide strong evidence that DE-associated cancer occurs in humans.</p>	<p>Do not use the rat data, since they are irrelevant to OEHHA's conjectured low-dose mechanisms.</p> <p>Do not claim that DE causes cancer in humans based on statistical associations that are not causal (see Table 4).</p>
<p>2. OEHHA's selection of cumulative exposure as a dose metric is not justified by experimental data in rats, which suggests that there is strong, nonlinear time-dependence and concentration-dependence in the observed cancer response.</p>	<p>The TSD's assumption of cumulative exposure is plausible and quite customary (C-OEHHA, p. 159)</p>	<p>Treat concentration and duration of exposure as two separate risk factors, rather than multiplying them together. The mechanism of high-dose rat lung cancer is not customary, and concentration-duration pairs with the same product may create very different risks.</p>
<p>3. OEHHA has selected inappropriate mathematical risk models that have not been validated and that ignore relevant mechanistic information (C-OEHHA-159-161)</p>	<p>The selected risk models are standard models from the TOX-RISK program. More realistic / accurate models are not. (C-OEHHA-161) Using model-free methods would depart from established practices in risk assessment. (C-OEHHA-162)</p>	<p>Use model-free estimation methods (Table 4) that do not require preconceived theories of carcinogenesis (since a correct theory for low doses is unknown.) The unusual mechanism of observed DE cancer induction justifies departing from established default practices.</p>
<p>4. OEHHA uses a retracted set of models that ignore the possibility of zero or negative responses at low doses.</p>	<p>Using a wider set of models is outside the realm of practicality (C-OEHHA, 164)</p>	<p>It is practical and easy with many nonlinear regression packages to consider a fuller range of possible models. Let the data pick the best model (which should include OEHHA's as one possibility).</p>
<p>5. The TSD ignores model uncertainty (C-OEHHA-164)</p>	<p>The models used in the TSD are the most plausible available. They are both generally accepted and widely used.</p>	<p>The TSD models are not widely used for DE cancer risk modeling, nor were they designed for DE. Use model-free estimation methods instead, since what is known about DE cancer mechanisms is not described by available models.</p>

TABLE 2: LUNG TUMOR RISKS (PREVALENCE AT DEATH) IN RATS CHRONICALLY EXPOSED TO DIESEL EXHAUST (Source: Mauderly *et al.*, 1987)

CONCENTRATION (mg/m ³)	ALL LUNG TUMORS*	
	Males	Females
0	0.01 = 2/182	0 = 0/182
0.35	0.005 = 1/184	0.01 = 2/183
3.5	0.02 = 4/182	0.02 = 4/182*
7	0.07 = 13/183*	0.09 = 16/181*

* = significantly elevated compared to control group (p < 0.05 based on chi-square test with Yates correction)

data set in which there does not appear to be a response threshold. Such statistical sleight-of-hand is now well understood. Aggregation can often be used to create statistical patterns that contradict the underlying truth that holds in each of the aggregated groups (see e.g., J. Gurland and J. Sethuraman, "How pooling failure data may reverse increasing failure rates", *Journal of the American Statistical Association*, 90, 432, 1995, 1416-1423, and references therein.) Proper procedure is to examine the dose-response pattern for each sex separately. If both sex-specific dose-response curves are consistent with the hypothesis of a concentration threshold for carcinogenic responses, as in Table 1, then the correct conclusion is that such a threshold is possible.

- **Premise 2.** All available scientific evidence is consistent with the hypothesis that the elevated risks observed at the highest dose levels in the Mauderly *et al.* experiment are explained by a non-chemical carcinogenic process, relevant only at high doses in which lung tissue is repeatedly damaged by mechanical abrasion from soot deposits that have not been cleared from the lung. Meanwhile, protective enzymes (such as GSH) that normally protect cells against the damage inflicted by such repetitive mechanical trauma are depleted by the very high, sustained exposures for which increases in lung tumors are observed. This mechanistic description fully explains the available data, but is presumably irrelevant at lower doses (Driscoll *et al.*, 1996; Nikula *et al.*, 1996).
- **Conclusion:** The elevated risks observed at the highest dose levels in the Mauderly *et al.* experiment are irrelevant to the question of whether tumors might occur at the much lower doses of practical interest, presumably by a different (e.g., genotoxic) mechanism. Although no such low-dose mechanism has been discovered for DE, despite vigorous and sophisticated searches (Driscoll *et al.*, 1996; Nikula *et al.*, 1996), its existence cannot be logically disproved by the failure to find it. But the Mauderly *et al.* data neither support nor refute conjectures about possible low-dose effects.

Thus, we recommend that the rat data not be used for purposes of drawing inferences about low-dose risks. OEHHA's claim that the rat data support their low-dose risk estimates is based on a statistically invalid aggregation of dose-response patterns across sexes.

2. OEHHA's selection of theoretical mathematical risk models for dose-response extrapolation is unjustified for the DE rat tumor data. Model-free methods such as nonparametric regression should be used instead. OEHHA has selected two mathematical risk models, the Weibull multistage and simplified Moolgavkar models, both of which are supported by the TOXRISK™ software package. However, neither model was designed to describe the events (e.g., lung over-burdening, repetitive lung tissue wounding, GSH depletion, proliferation of injured cells) that have been shown experimentally to be associated with tumorigenesis at the high DE concentrations where lung tumors occur. Moreover, both models lead to low-dose-linear dose-response relations -- an assumption that cannot be justified by the data and that tends to be undermined by the observed nonlinearities in the experimental rat data. Both models are generic -- they ignore the specific knowledge about high-dose DE carcinogenesis that are relevant for the data to which they are applied.

The key issue in model selection for DE is that standard models (such as the Weibull multistage and Moolgavkar models) were developed to describe different biological phenomena from those involved in experimental DE-induced rat lung carcinogenesis. OEHHA admits that low-dose responses would presumably be based on different, as-yet only conjectured, biological mechanisms. Therefore, there is no biological justification for pre-selecting the Weibull-multistage and Moolgavkar forms for purposes of extrapolating from the high-dose responses to hypothesized risks at lower doses. Modern statistical methods allow a range of practical, desirable alternatives, including not specifying any particular theorized parametric model in advance. This seems to be desirable, given that OEHHA frankly admits that low-dose mechanisms of DE carcinogenesis are unknown and speculative.

OEHHA could reduce the expected error introduced by its preselection of only two possible mathematical model forms by considering a wider range of risk models that allow for the possibility that the dose-response function is zero or sub-linear at sufficiently low doses. Practical ways to do this include the following:

- (a) *Model-averaging and model-weighting techniques* (Buckland *et al.*, 1997; Berger and Pericci, 1996). This approach deals with model uncertainty by allowing for a wide set of possible theoretical models and using the experimental data to judge their relative plausibility. Buckland *et al.* (1997) describe simple versions for use in applied work, directly addressing

OEHHA's expressed concerns about the complexity involved in doing a better job.

- (b) *Model-free estimation methods* e.g., nonparametric regression models (Hall and Turlach, 1997), model-free curve fitting, and computationally intensive smoothing methods that only require weak assumptions, e.g., that the dose-response curve be smooth, or that it be monotonic, or s-shaped, etc. These methods deal with uncertainty about the correct model by making very few assumptions and solving for the dose-response curve that best describes the empirical data points, without imposing any very strong theoretical preconceptions.
- (c) *Computationally intensive model selection methods* (e.g., Shao, 1996). This strategy searches for the dose-response model that minimizes estimated prediction errors, based on the available data.

However, OEHHA has chosen to consider only the Weibull multistage and simplified Moolgavkar models. In defending this choice, OEHHA states (p. 7-10) that "The analysis works with models that are considered to be the most plausible, and is not concerned with a mathematically complete set of alternatives that have no previous justification... However, the mathematical alternatives are difficult to rule out and may be considered to be a source of uncertainty." This reflects a misunderstanding of the nature of modern techniques such as model-free curve-fitting and nonparametric regression. The goal of these techniques is not to introduce unjustified alternatives to be ruled out, but rather to avoid introducing unnecessary theoretical assumptions in fitting dose-response curves to experimental data. As much as possible, the data should be allowed to determine the model that is used to describe the dose-response relation. It should select from a large set of *a priori* possibilities, with enough flexibility to adequately reflect the data (something that the Weibull multistage model has been criticized for not doing). Rather than either selecting or rejecting mathematical models that imply low-dose linearity *a priori*, for example, modern techniques attempt to let the experimental data determine the weight to be given to linear vs. nonlinear possibilities.

OEHHA does not know how (or whether) DE could cause cancer at low doses, so claiming that it has selected models that "are considered to be most plausible" (p. 7-10) is unwarranted. Many scientists, including Mauderly, have suggested that threshold or low-dose nonlinear models are more plausible than the ones that OEHHA has selected. When the most plausible models are not known, model-free techniques seem appropriate and should be used in addition to, or in preference to, pre-defined parametric models.

3. The data make it more likely than not that there is a DE concentration threshold below which lung tumor risks are not elevated in rats. Both

parametric and model-free methods give dose-response curves with this property when applied to either the male or the female rat data.

OEHHA claims that the rat data provide no evidence to support the hypothesis of a threshold for carcinogenic responses. This is an artifact of the way in which they have chosen to aggregate and model the data, and it contrasts with the interpretation of the original authors, who stated that (Mauderly *et al.*, 1987):

At the higher exposure levels, rats accumulated lung burdens of soot greater than those which would be predicted from results at the low exposure level. ... Vostal (1986) suggested that there is a threshold in the relationship between cumulative exposure (concentration x time) and this particle clearance "overload" phenomenon and that there should also be a threshold in the relationship between lung tumor incidence and dose (exposure concentration, cumulative exposure, or lung burden of soot). The results of the present study appear to support this hypothesis.

In defense of their model selection, OEHHA notes (p. 7-10) that "The high degree of non-linearity exhibited by the bioassays suggests that the use of [other, Armitage-Doll type] models would be impractical because of the complex calculations which would require estimation of many parameters. Other possible models might also give more accurate low-dose extrapolation... Such questions of model specification are a further source of uncertainty." In effect, OEHHA acknowledges that their risk models may be incorrect, but suggests that obtaining a more correct answer is too difficult to be practical.

In reality, however, it is easy to use widely available software packages to perform nonlinear regression modeling for a variety of nonlinear models that involve no more parameters than the models that OEHHA has selected in their Table 7-4. Doing so shows that, contrary to OEHHA's findings, the Mauderly *et al.* data set leads to positive threshold concentrations below which no excess risk is predicted, for both male and female rats, in multistage risk models no more complicated than those selected by OEHHA.

Figure 1 presents an example in which nonparametric regression (a simple distance-weighted least squares or loess algorithm) is used to fit a smooth curve to the male rat data in Table 2. In the absence of OEHHA's preconceived theoretical restrictions, this data-smoothing technique indicates no evidence whatsoever of increased tumor risk for male rates ("RISKMALE") at concentrations below about 2 mg/m³.

FIGURE 1: Nonparametric regression model for male rat data

FIGURE 1: Nonparametric regression model for male rat data

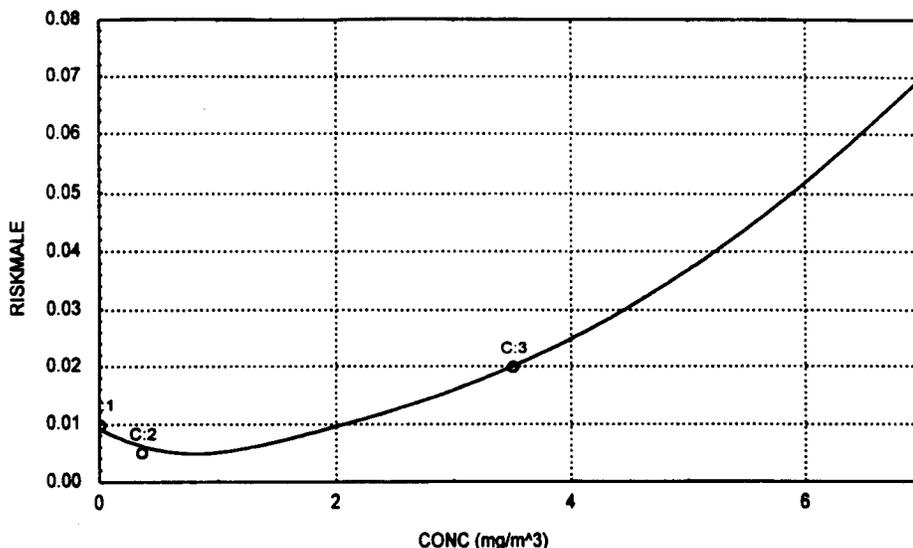


FIGURE 2: Data for Male Rats Show No Increase in Risk At Low Doses

FIGURE 2: Model: riskmale = r0 + r1*conc + r2*conc^2 + r3*conc^3
 $y = (0.01) + (-0.0168922) * x + (0.0076477) * x^2 + (-0.0005729) * x^3$

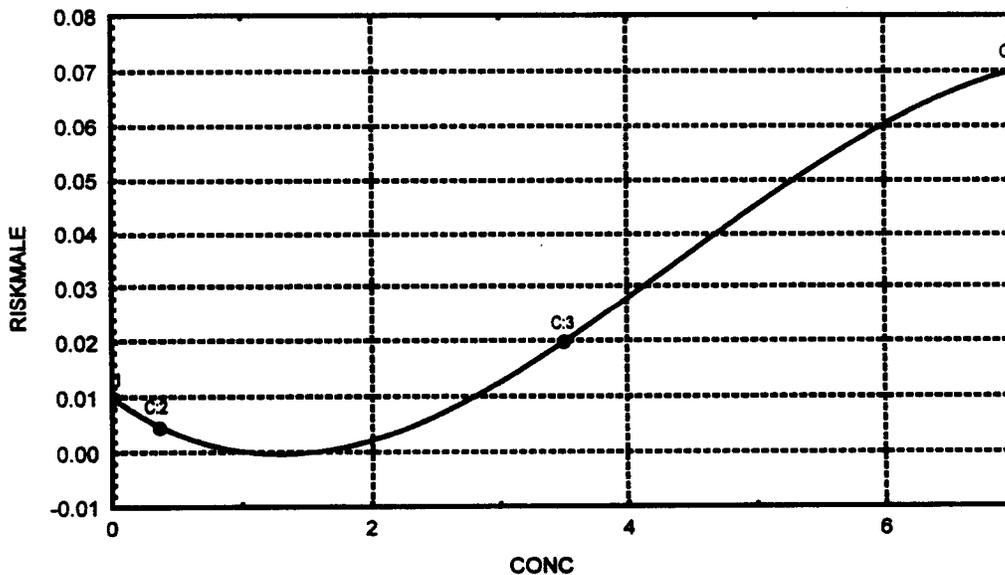


FIGURE 3: The Male Rat Data Show Evidence of a Non-Zero Threshold

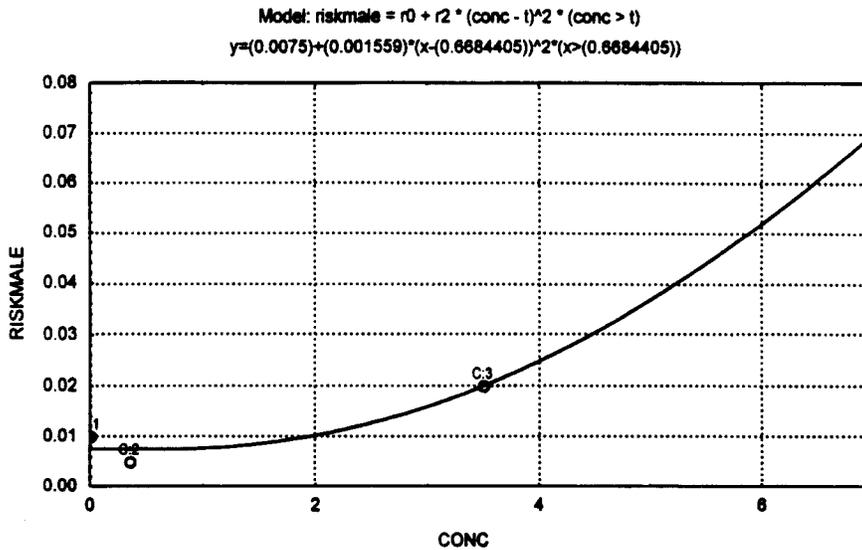
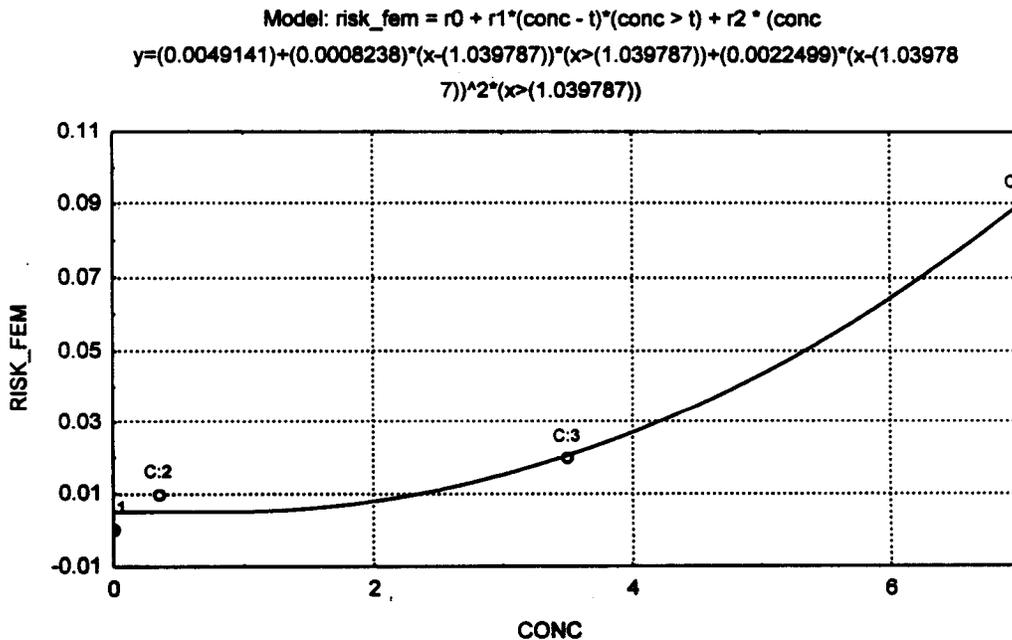


FIGURE 4: The Female Rat Data Also Show Evidence of a Non-Zero Threshold



Figures 2 and 3 show the results of applying parametric models to the same data set, while Figure 4 shows an analogous figure for the female rat data. Figures 3 and 4 allow for the possibility of a threshold, using the technique suggested by OEHHA in their Table 7.4 (p. 7-33). This technique allows for the possibility of a

threshold (indicated by an initial flat horizontal segment of the dose-response curve) and then estimates its value. If there is no threshold, the estimated value can be zero. Although OEHHA does not show the estimated value of the response thresholds in their tabulation of Weibull multistage model parameter estimates, our calculations (Figures 3 and 4) show a threshold between 1 and 2 for both male and female rats. (For male rats, attempts to include a positive linear term led to non-convergence of the estimation algorithm. Figures 1 and 2 suggest that this may be because no such term exists in reality.) Thus, in contrast to OEHHA's conclusions, the Mauderly *et al.* data suggest that a response threshold is not only possible, but is more plausible than OEHHA's assumption of low-dose linearity. Their claim to have used the "most plausible" models is therefore not supported by these data.

4. OEHHA's use of cumulative exposure as a dose metric to extrapolate high-dose tumor risks to low-dose risk is unreasonable. OEHHA extrapolates the low-dose linear models that it has fit to the aggregated Mauderly *et al.* rat data to project human risks by assuming that equivalent cumulative lifetime exposures create equivalent risks. But most tumors occur very late in the lives of affected rats. This poses a problem for the usual logic of cumulative-exposure extrapolation. If 7 mg/kg for one lifetime cause increased tumors in the last few weeks of life, then is it really plausible that 0.7 mg/kg for ten lifetimes would be expected to cause an equivalent increase in tumor risks in the last few weeks of life? Clearly not. The cumulative exposure hypothesis is not realistic because it would require extending exposure for several lifetimes to obtain equivalent risks. Less extremely, OEHHA's use of a cumulative dose metric ignores the age-dependence of tumor rates, and this appears to be an essential aspect of experimental tumors. Thus, OEHHA's assertion (C-OEHHA-159) that "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" is not justified for DE, as opposed to chemical carcinogens in general. Yet without it, the high-dose rat data cannot be extrapolated to much lower human exposures.

C. Risk Assessment Based on Reanalysis of the Garshick *et al.* Studies

A primary basis for OEHHA's quantitative risk assessment for DE is reanalysis of epidemiological data from the cohort and case-control studies of Garshick *et al.* As with the animal data, OEHHA has received and responded to many public comments on their analysis of these data, but its 1997 draft risk assessment remains very close in approach and results to the 1994 draft risk assessment.

Since publication of the studies, Garshick has updated his data and analysis, in part to remedy errors and omissions in the original data set, and has reported that the trend reported in his publications of increasing lung cancer risk with increasing cumulative exposure no longer holds (Garshick, 1991). Various investigators, most prominently Dr. Kenny Crump (1995), have argued that OEHHA's interpretation of the Garshick *et al.* data is not supported by the data. Other technical criticisms, summarized in Table 3, have been made, and either dismissed or discussed by OEHHA, but without changing the principle features of their approach or their most important conclusion -- that the data somehow justify an inference that DE exposure increases lung cancer risk in humans, and with a potency higher than in any other species.

In continuing hope of persuading OEHHA to use technically correct statistical methods to reanalyze the Garshick *et al.* data -- methods that do not ignore exposure uncertainties, that do allow for model uncertainty (including the possibility of nonlinearities at low doses, as well as the possibility of linearity), and that allow different individuals to have different dose-time-response relations, for example -- Table 4 recommends practical methods for overcoming the various technical statistical problems encountered in analyzing the Garshick *et al.* data set. The cited references provide algorithms and discuss available software packages that can carry out the required calculations without placing an excessive burden on OEHHA's staff. Table 5 outlines in more detail various factors that can create a statistical association between DE exposure and lung cancer in epidemiological studies such as those of Garshick's. All except the first (a true causal relationship) have been found and documented to hold in the Garshick *et al.* studies (e.g., Cox, 1997). Table 6 recommends appropriate formal statistical tests for whether observed statistical associations are causal. We urge OEHHA to apply these formal methods before drawing and promulgating policy-relevant conclusions about causation from epidemiological data, bearing in mind that there are many possible explanations for systematically elevated risk ratios (see Table 5) and that the Hill criteria (consistency, strength of association, biological plausibility, etc.) relied on in OEHHA's current draft "have not been as successful in sorting out the signal from the noise as might have been hoped some 30 years ago" in resolving the association-vs.-causation dilemma (N.E. Breslow, Statistics in Epidemiology: The Case Control Study", 1996 R.A. Fisher Lecture, *Journal of the American Statistical Association* **91**, 433, 14-28).

TABLE 3: Past Criticisms of OEHHA's Risk Assessment Based on the Garshick *et al.* Studies

CRITICISM	OEHHA's RESPONSE	REJOINDERS AND RECOMMENDATIONS
1. OEHHA's risk model begs the key question of low-dose nonlinearity and thresholds.	OEHHA maintains that the linear relative risk model is valid for purposes of quantitative risk assessment (C-OEHHA-167).	Let the data influence the weight given to different (e.g., linear vs. nonlinear) modeling possibilities (Lee 97, Gonzelez-Manteiga 96)
2. OEHHA's risk model ignores exposure measurement errors and uncertainties that can lead to inflated risk estimates.	In simple linear regression, the bias from neglected measurement error is downward. OEHHA expects biases to be small (< 10%) (C-OEHHA-168)	In threshold models, the bias is upward and can be large (Carroll, 1997). OEHHA should use a model with exposure uncertainties, since exposures are unknown.
3. OEHHA's model assumes that all individuals are equally susceptible to lung cancer. This is wrong and can bias risk estimates upward.	The reviewer has not presented a corrected analysis. It would complicate OEHHA's analysis to do so. OEHHA believes that an uncorrected model is adequate for their purposes (C-OEHHA-168)	Use appropriate statistical models (e.g., Ahn & Chen, 1997, Becker, 1997) that allow for interindividual heterogeneity. Abide by stated criteria for model adequacy (e.g., goodness-of-fit).
4. OEHHA uses cumulative exposure as a dose metric. This inconsistent with data on concentration vs. lung tumor.	The models used in the TSD are the most plausible available (C-OEHHA-164)	Treat exposure concentration and exposure duration as two separate factors in risk modeling. Let the data determine whether only their product affects risk; don't assume it.
5. OEHHA's own calculations indicate a threshold or strong nonlinearity in exposure-response. A nonlinear model (e.g., multistage model with no linear term) fits the data better with fewer parameters than OEHHA's straight-line model.	Four dose groups is too few to make it prudent to fit a nonlinear multistage model (C-OEHHA-167). Multistage theory predicts low-dose linearity. The Garshick exposure data are highly uncertain, justifying a forced linear model (C-OEHHA-170)	OEHHA routinely fits multistage models to data from 4 dose groups (e.g., the Mauderly <i>et al.</i> data.) Multistage theory may not apply to DE carcinogenesis. It does not justify fitting a straight line to nonlinear data. <i>Recommendation:</i> Pick the most appropriate model for the data via goodness-of-fit or other formal criteria (see Table 4), and/or use nonparametric regression.
6. OEHHA has only tested for statistical associations between DE exposure and lung cancer. They have not tested whether the associations are causal.	The TSD's new meta-analysis supports a dose-response relation bolsters the argument against alternative causes. Epidemiological studies indicate that DE-associated cancer is observed in humans. (C-OEHHA, p. 147, 152, 172.)	Apply relevant tests for causality (Table 6). The individual studies cited in the meta-analysis do not establish a causal relation between DE and lung cancer and do not test the hypothesis of alternative causes such as multiple comparisons bias.
7. OEHHA has not calculated or combined p-values correctly. Their analysis is flawed by multiple comparisons and multiple hypothesis testing.	Not addressed by OEHHA. (New to the meta-analysis.)	Correct for multiple hypothesis testing bias by using appropriate p-value adjustments (Efron, 1996; Toman, 1996; Westfall, 1997)
8. OEHHA has not resolved contradictory p-values in the literature.	Not discussed by OEHHA. (New to the meta-analysis.)	Re-estimate p-values using Bonferroni or other corrections for upward biases.

TABLE 4: SOME COMMON STATISTICAL PROBLEMS AND SUGGESTED MODELING AND DATA ANALYSIS METHODS FOR DEALING WITH THEM

STATISTICAL PROBLEM	APPROPRIATE METHOD	REFERENCES
Exposure estimation error and/or exposure classification errors	<ul style="list-style-type: none"> • Errors-in-variables models • Measurement error models 	Judge <i>et al.</i> , 1985; Stefanski and Cook, 1995; Nakamura, 1992 (for Cox model); Carroll, 1997
Interindividual heterogeneity in exposures or response parameters	<ul style="list-style-type: none"> • Mixture distribution models • Classification tree analysis • EM algorithm 	Lancaster, 1990 Ahn & Chen, 1997 Becker, 1997
<ul style="list-style-type: none"> • Model form unknown. • Linear model inappropriate. • Multi-way, nonlinear interactions among risk factors 	<ul style="list-style-type: none"> • Multivariate model-free methods (e.g., CART) • Nonparametric regression • Model selection techniques • Non-parametric survival data analysis 	Bacchetti & Segal, 1995 Ahn and Chen, 1997 Gasser & Kneip, 1995; Lee, 1996 Buckland <i>et al.</i> , 1997 Lin, 1997
False positives due to multiple comparisons / simultaneous hypothesis tests	Bonferroni-type adjustments of reported p-values. Monte-Carlo estimation of true p-values.	Biggs <i>et al.</i> , 1991, Efron, 1997 Westfall, 1997
False positives due to model selection bias	Cross-validation and other computational statistical methods for model selection and significance testing	Cheeseman & Oldford, 1994; Hjorth, 1994 Buckland <i>et al.</i> , 1997
Causal analysis of associations in multiple time series.	Granger-Sims causality tests	Granger, 1980; see also Table 1.
Causal analysis of multivariate associations among multiple risk factor and end-points	<ul style="list-style-type: none"> • Linear causal analysis • Nonlinear multivariate causal analysis via causal graphs and conditional independence relations • Non-experimental data analysis 	Kenny, 1979, Heise, 1975 Pearl, 1996; Yao and Tritchler, 1996; Shafer, 1996; Jensen, 1996. Swanson and Granger, 1997 Blalock, 1961; Campbell & Stanley, 1963
Attribution to DE of effects due to mixtures or interactions	Multivariate classification tree analysis	Biggs <i>et al.</i> , 1991; Michie <i>et al.</i> , 1994; Ahn and Chen, 1997
Aggregation errors from use of groups as units of analysis (Saari, 1987)	Survival data analysis using individual data	Lancaster, 1990; Lin, 1997; Bacchetti and Segal, 1995

TABLE 5: POSSIBLE SOURCES OF SIGNIFICANT POSITIVE ASSOCIATIONS BETWEEN DE AND LUNG CANCER IN THE GARSHICK ET AL. DATA SET

1. True causal relation: DE causes lung cancer: DE → lung cancer risk

2. Confounding: DE ← other factors → lung cancer. (DE = diesel exhaust exposure. "Other factors" may include year of birth, age at retirement, age at death, and so forth.)

3. Model selection bias: Investigators try different statistical models (e.g., various exposure groups, exposure assumptions, model formulas, and effect definitions) until one is found that yields a "significant" positive relation. Using the data to select models may create false positives (Buckland *et al.*, 1996; Hjorth, 1994)

4. Multiple comparisons bias: Investigators examine many subsets of variables (pollutants, seasons, weather conditions) and subsets of people (by ages, medical status, etc.) until "significant" positive relations are found.

5. Extrapolation and attribution biases: A statistical model (linear, logistic, or Poisson regression; proportional hazards, etc.) is used that falsely attributes positive effects at high concentrations and/or due to synergy among multiple factors to lower concentrations and/or to DE.

6. Sampling, selection, recall, and reporting biases: Investigators interview subjects (e.g., families of deceased workers) who may not represent the population for which inferences are drawn.

TABLE 6: SOME FORMAL TESTS FOR CAUSALITY

DATA	HYPOTHESIS TESTED	TEST	PRINCIPLE
Two time series	TEMPORAL CAUSATION: The association between two time series is causal.	Granger-type tests (Granger, 1980; Sims, 1990; Boudjellaba, 1992; Hosoya, 1997)	The cause occurs before the effect and contains unique information about it.
Multiple variables in multiple periods	EXOGENEITY: A variable is determined from outside a system of equations (i.e., from outside a model)	Tests for exogeneity (Geweke, 1984; Ericsson and Irons, 1994)	Future values of exogenous variables do not help to predict past values of endogenous ones.
Multiple variables, enough observations to calculate joint and conditional frequency distributions.	CONDITIONAL INDEPENDENCE: One set of variables (e.g., health effects) is conditionally independent of a set of proposed causes, given the values of intervening variables.	Directed graph tests, tests for d-separation (Jensen, 1996; Pearl, 1996; Shafer, 1996; Yao and Tritchler, 1996).	If X causes Y and Y causes Z, then the positive association between X and Z should disappear when conditioned on the level of Y.
Correlations among multiple variables	PATH COEFFICIENTS: A model (system of linear equations relating variables) is consistent with a postulated causal structure, represented by a path diagram.	Path analysis (for linear models) (Heise, 1975; Kenny, 1979; Yao and Tritchler, 1996) See also Swanson & Granger, 1997.	Linear effects are transmitted along directed arrows in a causal graph from some variables to others.
Multi-equation model relating values of variables	CAUSAL ORDERING: One variable precedes another in the causal graph showing what is determined from what.	Simon-type algorithms for partial causal ordering of model variables (Simon, 1977; Yao and Tritchler, 1996)	Some subsets of variables suffice to determine their own values and the values of other variables. Thus, a system of equations creates a causal partial ordering among variables.

Reanalysis of the Garshick *et al.* study data using conditional independence tests (see Table 6) shows that any statistical association between DE concentration and lung cancer risk is not causal, insofar as lung cancer risk is conditionally independent of DE exposure concentration, given the values of other (specifically, age-related) variables.

OEHHA has already expressed little enthusiasm for using technically correct methods (described by OEHHA as "mathematically more complete") to obtain more informative and probably more accurate risk estimates, on the grounds that doing so "would unnecessarily complicate the TSD's presentation" (C-OEHHA-163). Nor have they been anxious to rigorously test their key hypotheses, e.g., by letting the data determine how much weight should be given to different possible models. Instead, they have observed that assumptions "would no longer be assumptions" if they were tested, and that they believe in their current conclusions without seeing any need for formal testing. Therefore, it seems likely that they will not heed the recommendations or apply the methods identified in Tables 3-6.

The following points are intended to establish that, in the absence of further analysis, the Garshick *et al.* data do not support OEHHA's conclusions of a positive relation – either statistical or causal – between DE exposure and human cancer risk.

1. OEHHA claims (p. 7-15) that "The quantitative risk assessments below derive slopes that estimate the increase in cancer risk for increase in diesel exhaust exposure." This causal interpretation of statistical associations is unwarranted. OEHHA has not shown that an increase in diesel exhaust exposure would increase human cancer risk. Instead, they only describe statistical associations. Such associations are not evidence of causation: they might be expected to occur whether or not there is a causal association, for the reasons listed in Table 5. Interpreting statistical associations as evidence of causation without testing this assumption rigorously (see Table 6) does a disservice to decision-makers, as the purported link between changes in DE exposure and resulting changes in public health impacts has not been established.

2. The hypothesis of a causal relation is not supported by the Garshick *et al.* cohort study. The Garshick *et al.* (1988) study involves many sets of variables that are mutually correlated. For example, worker age at death is positively associated with both average DE concentration and with lung cancer incidence rate. When the confounding effects of such associations are removed, there is no remaining (potentially causal) association between DE concentration and lung cancer (Cox, 1997). Details were sent to OEHHA's Dr. Stan Dawson (personal communications from Dr. Tony Cox) in 1995. Dr. Kenny Crump has independently arrived at a similar conclusion using different methods. OEHHA's

insistence that the Garshick *et al.* study supports their conclusions and causal interpretations is not objectively warranted by the data.

3. Concentration of DE is not positively associated with lung cancer risk in the Garshick *et al.* (1988) study. Indeed, it has a non-significant negative association. This undermines any plausible causal interpretation of DE as a human lung carcinogen. OEHHA obscures this fact by only discussing *cumulative exposure* as an indicator of DE exposure history. Since duration of employment is positively associated with lung cancer, OEHHA is able to hide the non-positive association between DE concentration and cancer risk behind the overall positive association between cumulative exposure (to DE and all other concurrent occupational factors, based on duration) and lung cancer.

It is easy to regress individual lung cancers against multiple factors, including estimated duration and average concentration of DE exposure, to estimate their separate contributions. (As discussed in Cox, 1997, the actual relations among variables are nonlinear in several cases, so that multiple linear regression is only a useful starting point.) Table 7 summarizes the results of multiple linear regressions in which each variable in the first column is regressed against the other column variables. The numbers are standardized beta coefficients, indicating the estimated contribution of each independent variable to each dependent variable while linearly adjusting for the contributions of the other variables. Coefficients not in parentheses are highly statistically significantly different from zero. (When an F-test is used to select variables for inclusion in the model via standard forward subset selection, the variables without significant coefficients in Table 7 drop out, but the remaining coefficients are almost unchanged.) Inspecting the row for CONC (= estimated average DE exposure concentration) shows that it is not significantly positively associated with LUNG1 (human lung cancer). Year of retirement (RET) is positively associated with both DE exposure (DURATION and CONC) and with lung cancer. More general nonlinear analysis (Cox, 1997) shows that age at death is also positively associated with lung cancer risk, as well as with DE exposure concentration; thus, death age is a confounding factor that could provide a non-causal explanation of any positive statistical association between DE exposure and lung cancer. OEHHA's data analysis has not accounted for such confounding effects, undermining their causal interpretation of the epidemiological data.

TABLE 7: MULTIPLE LINEAR REGRESSION MODELS FOR THE GARSHICK *ET AL.* COHORT STUD

<u>DEPENDENT</u>	AGE59	RET	DURATION	CONC	DEATHAGE	LUNG1	R ²
AGE59	—	-0.25	-0.10	0.84	0.04		0.98
RET	-0.28	—	0.88	0.18	0.06	0.003	0.98
DURATION	-0.12	0.95	—	0.14	-0.03	(-0.0004)	0.98
CONC	1.06	0.20	0.14	—	0.05	(-0.001)	0.97
DEATHAGE	0.47	0.59	-0.25	0.47	—	(-0.04)	0.76
LUNG1	(0.08)	0.112	(-0.02)	(-0.04)	(-0.02)	—	0.004

Source: Cox, 1997

4. OEHHA's own analysis of the Garshick et al. data indicates that a threshold model is much more plausible than a linear low-dose model for human data. Figure 7-3, page 7-46 of the draft risk assessment shows that relative risks do not increase for the three lowest cumulative exposures, but increase dramatically for the fourth. This data pattern is consistent with a threshold model: the observed pattern fits the definition of a response threshold perfectly, but provides a relatively poor fit to the linear model (indicated by the straight line in Figure 7-3) assumed by OEHHA.

OEHHA suggests that the Garshick *et al.* data support a linear model over a threshold model and that "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 evidence of real sublinearity" (C-OEHHA-170). These suggestions are flatly contradicted by the data. Formal statistical tests confirm what is visually apparent in Figure 7-3: that a threshold model fits the data significantly better than a linear model. OEHHA responds that "consistent with the theoretical constraint", a linearized multistage model would (by definition) include a positive low-dose linear component (*ibid.*). But there is no theoretical constraint in the multistage model that requires a positive linear term. The linearity that OEHHA refers to as a "theoretical constraint" is imposed as a regulator's convention (unjustified by statistical theory) in constructing confidence bands. In truth, if a nonlinear (e.g., purely quadratic or cubic) model were known to be correct, then correctly computed upper confidence limits would not be linear, but would approach zero at the origin.

OEHHA's risk model and calculations (Table 7.10) are highly idiosyncratic. The use of log-transformed relative risks and simple linear regression are not standard in risk analysis and have no obvious biological rationale. Rejecting better-fitting threshold and sub-linear models *a priori* in favor of an *ad hoc* log-linear model appears to violate OEHHA's own espoused principle of using goodness-of-fit in model selection and evaluation.

In summary, we recommend that OEHHA not enforce a straight-line fit to the nonlinear data. This methodological choice drives the rest of their risk analysis. It is based purely on an *ad hoc* assumption rather than on data or sound, clearly applicable theory. A better, equally practical alternative would be *model-averaging* (Buckland *et al.*, 1997), in which the true form of the relationship between exposure and response is treated (realistically) as unknown, and the data are used to weight different possible options, including linear and nonlinear possibilities.

Finally, how much numerical difference would a more flexible modeling approach be expected to make in OEHHA's quantitative risk estimates based on the Garshick data? As a very rough approximate bound, suppose that there are *k* alternative models that are considered at least as plausible as OEHHA's linear

model. If these alternative models specify zero increased risk at low doses, then OEHHA's risk estimate should be reduced by at least $1/k$ (and further if the alternatives are more plausible than the linear model). In our opinion, a value of at least $k = 4$ is realistic, since there are at least three alternative models (quadratic, cubic, and threshold) that are at least as plausible as OEHHA's linear model. Thus, we would expect that accounting for model uncertainty in the Garshick data reanalysis via model-averaging would reduce OEHHA's risk estimates (MLE and UCL) by at least a factor of 4.

D. Risk Estimates Based on Meta-Analysis

OEHHA claims that its analysis and interpretation of the Garshick *et al.* data are bolstered by a meta-analysis of many other epidemiological studies. However, their meta-analysis is flawed in its treatment of significance levels and in its approach to causal evidence and interpretation. The purpose of this section is to explain why the meta-analysis provides no support for OEHHA's conclusions and fails to bolster the rest of the risk assessment.

1, OEHHA's claim that "Support for the finding of a carcinogenic effect of diesel exhaust also comes from the meta-analysis in Appendix D" (C-OEHHA-152) is not justified. The meta-analysis deals only with statistical associations, rather than with cause and effect. No statistical tests for causation have been performed (see Table 6). The individual studies cited by OEHHA in their meta-analysis suffer from the artifacts listed in Table 5, so that they are expected to produce false positives (and hence the appearance of a small but consistent pattern of elevated risks in exposed populations) even in the absence of a causal relation between them. Thus, observing such a pattern provides no evidence of a causal association between DE exposure and lung cancer.

2. OEHHA (p. 6-47) notes that point estimates of relative risk tend to exceed 1 in many studies of DE exposure and cancer risk and states that "If these findings were due to chance, one would expect a more nearly equal distribution of point estimates of risk above and below unity." This is an error. It confuses findings being "due to chance" with findings being "unbiased" (equally likely to fall above or below 1). Findings due entirely to chance may nonetheless contain biases that tend to make them systematically fall above 1 rather than below it. For example, most investigators, as well as OEHHA in its meta-analysis, have engaged in "subset analysis" in which multiple subsets of workers are examined (e.g., based on age, job category, duration of exposure, etc.) and those subsets that produce statistically significant positive associations are reported. However, such analyses tend to systematically produce false positives (point estimates above 1) unless statistical significance levels are reduced to control for multiple comparisons / multiple hypothesis testing bias. Statistical techniques for appropriately reducing significance levels

are available (e.g., simple, approximate Bonferroni inequality adjustments or more sophisticated and accurate Monte-Carlo methods) but do not appear to have been used by OEHHA or in the individual studies included in OEHHA's meta-analysis. Therefore, false positives due to chance alone (in conjunction with improper setting of p-values and confidence limits) are expected to produce a consistent tendency for relative risks to be greater than 1 in the studies examined by OEHHA. OEHHA is mistaken in claiming that this observed pattern is evidence against a chance explanation.

As a second example of how findings due to chance alone can systematically tend to produce relative risks greater than 1, suppose that exposure has no effect on cancer risk but that there is some heterogeneity in individual cancer risks. For example, suppose that the probability of death with lung tumor is 0.2 among sensitive people and 0.1 otherwise, and that half the population is sensitive (independent of DE exposure). Randomly matching exposed individuals with similar unexposed controls and computing relative risk would give four possible relative risk ratios: $0.2/0.2 = 1$, $0.1/0.2 = 0.5$, $0.2/0.1 = 2$, and $0.1/0.1 = 1$. These four outcomes are equally likely, since the distribution of risks is identical in the exposed and unexposed populations. Hence, the average relative risk obtained from a large number of such matchings will be $(1 + 0.5 + 2 + 1)(1/4) = 4.5/4 = 1.125$. In other words, the point estimate of the relative risk exceeds 1 even though exposure has no effect on risk. This simple example illustrates a principle that holds more generally: relative risk calculations that ignore heterogeneity in individual response probabilities within groups may be biased upward. Both OEHHA's proposed models and the risk models used in key studies relied on by OEHHA (such as those of Garshick *et al.*) make this mistake.

1. **OEHHA states (p. 6-47) that "In the studies with the more complete diesel-related exposure and duration of employment information, several identified exposure-response relationships, including the two studies by Garshick *et al.*" But no such exposure-response relationships have been unambiguously identified.** For example, in their cohort study, Garshick *et al.* (1988, p. 823) conclude that "In this study we demonstrate an association between diesel exhaust exposure and lung cancer." However, as described by the authors, "With recent exposure included, no evidence of a consistent exposure duration-response relationship was obtained... When exposure in the year of death and the 4 years before were disregarded... the group with at least 15 years of exposure (with current exposure not included) had a relative risk of lung cancer of 1.72 (95% CI = 1.27, 2.33)", emphasis added.) For the authors to exclude the most recent four years worth of data is an *ad hoc* truncation of the data that generates a positive result in this study but not in the case-control study, where "the relative odds ratio of lung cancer decreased slightly with recent exposure disregarded" (*ibid.*, p. 823). A positive result created only by selectively discarding data (or, equivalently, selecting a subset of the data to

analyze), with the selection being made differently in different studies to maximize positive results, clearly runs the risk of being a false positive. For OEHHA to assert that such ambiguous evidence "identified an exposure-response relationship" is misleading.

It is also misleading to characterize the two studies of Garshick *et al.* as having "more complete diesel-related exposure information", since no exposure information whatsoever was available for the individuals in these studies. The apparent exposure-response relationship may be due partly to ignored exposure measurement error (Carroll, 1997). OEHHA has deliberately refused to use appropriate measurement-error models. [See page C-OEHHA-168. Here, a discussion of measurement errors in simple linear regression models of doubtful relevance to binary outcomes (lung cancer or no lung cancer) is followed by the statement that "OEHHA staff, then, do not agree that the realism of the present approach needs to be improved" by allowing for exposure measurement errors.]

5. OEHHA states (p. 6-48) that "The meta-analysis identified evidence of exposure-response relationships in the subgroup analyses based on duration of exposure." The claimed relationships are likely outcomes of improper statistical methodology in the individual studies – something that OEHHA should have identified and discussed in deciding which studies to include in their meta-analysis. For example, Garshick *et al.* (1986, p. 1242) report that, in their case-control study, "Workers 64 years of age or younger at the time of death with work in a diesel exhaust exposed job for 20 years had a significantly increased relative odds (odds ratio = 1.41, 95% CI = 1.06, 1.88) of lung cancer." This presumably contributes to OEHHA's claimed "evidence of exposure-response relationships." But is it based on unsound analysis. The statement is an instance of a whole family of statements of the form "Workers who were A years or younger at the time of death and who were exposed to diesel exhaust for Y years had a significantly increased relative odds ratios for lung cancer." The probability of at least one false positive occurring among the multiple hypotheses in this family corresponding to different combinations of A (e.g., no more than 54, 59, 64, 69, 74, 79, etc. years old at death) and durations of exposure (e.g., Y = 5, 10, 15, 20, 25, etc. years) is not limited to 5% when each combination of A and Y values is tested at a p = 5% significance level. For example, if 30 different (A, Y) combinations are considered, each independently having a 5% probability of a false positive (i.e., a reported 5% significance level), then the probability of at least one false positive occurring in the study as a whole is $p = 1 - (1 - 0.05)^{30} = 78\%$. This p-value for the whole study is more than 15 times greater than the reported significance level of 5%. OEHHA cites such results as evidence for a statistically significant (or causally significant) exposure-response relationship without noting that p-values in the individual studies have not been correctly calculated. They have been inadequately critical in selecting results for inclusion in their meta-analysis.

E. Causation Not Demonstrated

Consideration of the above-noted topics leads to a different set of conclusions than those obtained by OEHHA. The final conclusion articulated by OEHHA, that of a probable causal link between DE exposure and human lung cancer, does not follow from application of data-driven analyses, as described above and as summarized here. OEHHA's draft risk assessment for DE asserts that the Mauderly *et al.* rat data, the Garshick *et al.* human data, and multiple studies considered in their meta-analysis provide mutually consistent evidence of a no-threshold dose-response relation, implying that low levels of DE increase human lung cancer risks in proportion to cumulative exposure. Our reexamination of these three data sources reveals opposite conclusions. The rat data provide stronger evidence for a threshold relation than for OEHHA's low-dose linear models, precisely as stated by the original investigators. The Garshick *et al.* data as analyzed by OEHHA also suggest a threshold model much more strongly than a linear model. A reanalysis of the Garshick *et al.* cohort data using concepts of causal analysis shows that there is no causal association between DE and lung cancers. The studies in the meta-analysis are ambiguous and provide no clear evidence for or against the hypothesis of a causal link between DE exposure and human lung cancer risk. Thus, OEHHA's claims that their risk estimates are backed by multiple sources of data and evidence is unjustified. Their risk assessment is entirely dominated by one extreme assumption -- that relative risks are related to cumulative exposure by a straight line. This key assumption lacks theoretical or biological justification and is contradicted by both the animal and the human data. If the data were used to help select appropriate risk models, then the best-supported models would predict a threshold or low-dose sub-linear dose-response relationship, implying that DE does not create a human health risk at the exposure levels of interest. Any other conclusion reflects prior convictions or untested assumptions rather than available facts and data.

G. REFERENCES ON STATISTICS AND CAUSATION

- Ahn, H., and J.J. Chen, 1997. Tree-structured logistic model for over-dispersed binomial data with application to modeling developmental effects. *Biometrics*, 53, 435-455.
- Bacchetti, P., and M.R. Segal, 1995. Survival trees with time-dependent covariates: Application to estimating changes in the incubation period of AIDS. *Lifetime Data Analysis*, 1, 1, 35-48.
- Becker, N.G., Uses of the EM algorithm in the analysis of data on HIV/AIDS and other infectious diseases. *Stat Methods Med Research*, 6, 1, 24-37.
- Berger, J.O., and L.R. Pericchi, 1996. The intrinsic Bayes factor for model selection and prediction. *JASA*, 91, 433, 109-122
- Breslow, N.E., 1996. Statistics in Epidemiology: The Case Control Study. *Journal of the American Statistical Association* 91, 433, 14-28.
- Buckland, S.T., K.P. Burnham, and N.H. Augustin, 1997. Model selection: An integral part of inference. *Biometrics*, 53, 603-618.
- Biggs, D., B. de Ville, E. Suen, 1991. A method of choosing multiway partitions for classification and decision trees. *J. Applied Statistics*, 18, 1, 49-62.
- Blalock, H.M., 1961. *Causal Inferences in Nonexperimental Research*. University of North Carolina Press, Chapel Hill.
- Boudjellaba, H., J.-M. Dufour, and R. Roy, 1992. Testing causality between two vectors in multivariate autoregressive moving average models. *Journal of the American Statistical Association*, 87, 1082-1090.
- Buckland, S.T., K.P. Burnham, N.H. Augustin, 1997. *Model selection: An integral part of inference*. *Biometrics*, 53, 603-618.
- Campbell, D.T., and J.C. Stanley, 1963. *Experimental and Quasi-Experimental Designs for Research*. Rand McNally, Chicago.
- Carroll, R.J., 1997. Surprising effects of measurement error on an aggregate data estimator. *Biometrika*, 84, 1, 231-134.
- Cheeseman, P. and R.W. Olford (Eds.), 1994. *Selecting Models from Data*. Springer-Verlag, *Lecture Notes in Statistics*, Volume 89, pp. 339-350. New York.
- Cox, L.A., Jr., 1997 Does diesel exhaust cause human lung cancer? *Risk Analysis*. (Forthcoming)
- Efron, B., 1997. The length heuristic for simultaneous hypothesis tests. *Biometrika*, 84, 1, 143-157.

- Ericsson, N.R., and J.S. Irons (eds), 1994. *Testing Exogeneity*. Oxford University Press, Oxford, England.
- Gasser, T., and A. Kneip, 1995. Searching for structure in curve samples. *Journal of the American Statistical Association*, **90**, 432, 1179-1187.
- Geweke, J., 1984. Inference and Causality. Ch. 19 in Z. Griliches and M.D. Intriligator (Eds.), *Handbook of Econometrics*, Vol. 2. North-Holland, Amsterdam.
- Granger, C.W.J., 1980. Tests for causation -- a personal viewpoint. *Journal of Economic Dynamics and Control*, **2**, 329-52.
- Granger, C.W.J., and P. Newbold, 1974. Spurious Regression in Econometrics. *Journal of Econometrics* **2** (2), 111-120.
- Gurland, J., and J. Sethuraman, 1995. "How pooling failure data may reverse increasing failure rates", *Journal of the American Statistical Association*, **90**, 432, 1416-1423.
- Hall, P., and B.A. Turlach, 1997. Interpolation methods for adapting to sparse designs in nonparametric regression. *Journal of the American Statistical Association*, **92**, 438, 466-472.
- Heise, D.R., 1975. *Causal Analysis*. Wiley, New York.
- Hill, P., and B.A. Turlach, 1997. Interpolation methods for adapting to sparse design in nonparametric regression. *Journal of the American Statistical Association*, **91**, 433, 109-122
- Hjorth, J.S. Urban, 1994. *Computer Intensive Statistical Methods: Validation, Model Selection, and Bootstrap*. Chapman & Hall.
- Hosoya, Y., "Causal analysis and statistical inference on possibly non-stationary time series." Chapter 1 in D.M. Kreps and K.F. Wallis (Eds), *Advances in Economics and Econometrics: Theory and Applications*. Volume III. Cambridge University Press, 1997.
- Jensen, F.V. *An Introduction to Bayesian Networks*. Springer, 1996.
- Judge, G.C., W.E. Griffiths, R.C. Hill, H. Lutkepohl, and T-C Lee, 1985. *The Theory and Practice of Econometrics: Second Edition*. Wiley, New York.
- Kenny, D.A., 1979. *Correlation and Causality*. Wiley, New York.
- Lancaster, T. 1990. *The Econometric Analysis of Transition Data*. Cambridge University Press, New York.
- Lee, C.C., 1996. On estimation for monotone dose-response curves. *Journal of the American Statistical Association*, **91**, 435, 1110-1119.
- Lin, D.Y., 1997. Non-parametric inference for cumulative incidence functions in competing risks studies. *Statistics in Medicine*, **16**, 901-910.

Michie, D., D.J. Spiegelhalter, and C.C. Taylor (Eds.), 1994. *Machine Learning, Neural and Statistical Classification*. Ellis Horwood Series in Artificial Intelligence. Ellis Horwood.
Nakamura, T., 1992. Proportional hazards model with covariates subject to measurement error. *Biometrics* **48**, 829-638.

Nelson, C.R. and G.W. Schwert, 1982. Tests for predictive relationships between time series variables. *Journal of the American Statistical Association*, **77**, 11-18.

Pearl, J., 1996. A causal calculus for statistical research. Chapter 3 in D. Fisher and H-J Lenz (Eds), *Learning from Data: Artificial Intelligence and Statistics V*. Springer-Verlag, New York.

Raferty, A.E., D. Madigan, J.A. Hoeting, 1997. Bayesian model averaging for linear regression models. . *Journal of the American Statistical Association*, **92**, 437, 179-191.

Saari, D.G., 1987. The sources of some paradoxes from social choice theory and probability. *Journal of Economic Theory*, **41**, 1-22.

Shafer, G., 1996. *The Art of Causal Conjecture*. MIT Press. Cambridge, MA.

Shao, J., 1996. Bootstrap model selection. *JASA*, **92**, 438, 466-472.

Simon, H.A., 1977. Causes and Possible Worlds. Section 2 in H.A. Simon, *Models of Discovery*. Dordrecht: D. Reidel.

Sims, C.A., Multivariate time series models. In J. Eatwell, M. Milgate, and P. Newman (Eds.) *The New Palgrave Time Series and Statistics*. W.W. Norton and Company. New York, 1990.

Stefanski, L.A., and J.R. Cook, 1995. Simulation-Extrapolation: The Measurement error Jackknife. *Journal of the American Statistical Association*, **90**, 432, 1247-1256.

Swanson, N.R., and C.W.J. Granger, 1997. Impulse response functions based on a causal approach in residual orthogonalization in vector autoregressions. *Journal of the American Statistical Association*, **92**, 437, 357-367.

Westfall, P., 1997. Multiple testing of general contrasts using logical constraints and correlations. . *Journal of the American Statistical Association*, **92**, 437, 299-306.

Yao, Q. and D. Tritchler, 1996. Likelihood-based causal inference. Chapter 4 in D. Fisher and H-J Lenz (Eds), *Learning from Data: Artificial Intelligence and Statistics V*. Springer-Verlag, New York.

OTHER REFERENCES

- Ahlberg, J., A. Ahlborn, H. Lipping, S. Norell, L. Osterblom, 1981. Cancer among professional drivers: A problem-oriented register-based study. *Lakartidningen*. 78:1545-1546.
- Bacchetti, P., and M.R. Segal, 1995. Survival trees with time-dependent covariates: Application to estimating changes in the incubation period of AIDS. *Lifetime Data Analysis*, 1, 1, 35-48.
- Bender, A.P., D.L. Parker, R.A. Johnson, W.K. Scharber, A.N. Williams, M.C. Marbury, J.S. Mandel, 1989. Minnesota highway maintenance worker study: Cancer mortality. *American J. of Industrial Medicine*. 15:545-556.
- Biggs, D., B. de Ville, E. Suen, 1991. A method of choosing multiway partitions for classification and decision trees. *J. Applied Statistics*, 18, 1, 49-62.
- Blalock, H.M., 1961. *Causal Inferences in Nonexperimental Research*. U. North Carolina Press, Chapel Hill.
- Breiman, L., J. Friedman, R. Olshen, C. Stone, 1984. *Classification and Regression Trees*. Wadsworth Publishing.
- Burns, P.B., and G.M. Swanson, 1991. The Occupational Cancer Incidence Surveillance Study (OCISS): Risks of lung cancer by usual occupation and industry in the Detroit metropolitan area. *American Journal of Industrial Medicine*. 19:655-671.
- California Environmental Protection Agency, 1994. Draft Health Risk Assessment for Diesel Exhaust. Office of Environmental Health Hazard Assessment.
- Campbell, D.T., and J.C. Stanley, 1963. *Experimental and Quasi-Experimental Designs for Research*. Rand McNally, Chicago.
- Charnes, J.M., and P.P. Shenoy, 1997. A forward Monte-Carlo method for solving influence diagrams using local computation. Paper presented at the Sixth International Workshop on Artificial Intelligence and Statistics. January 4-7, Fort Lauderdale, Florida. (To be published in proceedings volume – information to be obtained.)
- Cohen, A.J., and M.W.P. Higgins, 1995. Health effects of diesel exhaust: Epidemiology. In Diesel Exhaust: A Critical Analysis of Emissions, Exposure, and Health effects. A Special report of the Institute's Working Group. Health effects Institute (HEI), Cambridge, MA.
- Cohen, P.R., D.E. Gregory, L. Ballesteros, and R. S-Amant. Two algorithms for inducing structural equation models from data. Chapter 1 in D. Fisher and H-J Lenz (Eds), *Learning from Data: Artificial Intelligence and Statistics V*. Springer-Verlag, New York.
- Cox, L.A., Jr., 1997 Does diesel exhaust cause human lung cancer? *Risk Analysis*. (Forthcoming)
- Cox, L.A., Jr., 1996. Using causal knowledge to learn more useful decision rules from data. Chapter 2 in D. Fisher and H-J Lenz (Eds), *Learning from Data: Artificial Intelligence and Statistics V*. Springer-Verlag, New York.
- Cox, L.A., Jr., "Managing uncertain risks through 'intelligent' classification: A combined artificial intelligence/decision analysis approach," pp 473-482 in J.J. Bonin and D.E. Stevenson (eds), *Risk Assessment in Setting National Priorities*. Plenum Press, New York, 1989.
- Crump, K.S., T. Lambert, and C. Chen, 1991. Assessment of risk from exposure to diesel engine emissions. Report prepared for the U.S. Environmental Protection Agency, Office of Health Assessment, by Clement International Corporation, Ruston, Louisiana (Work Assignment No. 182, July).

Crump, K.S., 1995. Letter to EPA Project Manager, dated May 12, 1995.

Damber, L.A., and L.G. Larsson, 1985. Professional driving, smoking, and lung cancer: A case referent study. *British Journal of Industrial Medicine*. 42:246-252.

Dawson, S.V., 1995. Letter to EPA Project Manager, dated April 27, 1995.

Driscoll, K.E., J.M. Carter, B.W. Howard, D.G. Hassenbein, W. Pepekko, R.B. Baggs, and G. Oberdorster, 1996. Pulmonary inflammatory, chemokine, and mutagenic responses in rats after subchronic inhalation of carbon black. *Toxicology and Applied Pharmacology*, 136, 372-380.

Edling, C., C.. Anjou, O. Axelson, H. Kling, 1987. Mortality among personnel exposed to diesel exhaust. *International Archives of Occupational and Environmental Health*. 59:559-565.

Elder, J. and D. Pregibon, 1996. A statistical perspective on knowledge discovery in databases. Chapter 4 in U.M. Fayyad, G. Piatetsky-Shapiro, P. Smyth, and R. Uthurusamy (Eds.), *Advances in Knowledge Discovery and Data Mining*. AAAI Press/The MIT Press, 1996.

Emmelin, A., L. Nystrom, S. Wall, 1993. Diesel exhaust exposure and smoking: A case-referent study of lung cancer among Swedish dock workers. *Epidemiology*. 4:237-244.

Fayyad, G. Piatetsky-Shapiro, P. Smyth, and R. Uthurusamy (Eds.), *Advances in Knowledge Discovery and Data Mining*. AAAI Press/The MIT Press, 1996.

Fisher, D. and H-J Lenz (Eds), 1996. *Learning from Data: Artificial Intelligence and Statistics V*. Springer-Verlag, New York.

Garshick, E., M.B. Schenker, A. Munoz, M. Segal, T.J. Smith, S.R. Woskie, S.K. Hammond, F.E. Speizer, 1987. A case-control study of lung cancer and diesel exhaust exposure in railroad workers. *American Review of Respiratory Diseases*, 135, 1242-1248.

Garshick, E., M.B. Schenker, A. Munoz, M. Segal, T.J. Smith, S.R. Woskie, S.K. Hammond, F.E. Speizer, 1988. A retrospective cohort study of lung cancer and diesel exhaust exposure in railroad workers. *American Review of Respiratory Diseases*, 137, 820-825.

Garshick, E., 1991. Letter to Dr. Chao Chen (U.S. EPA), dated August 15, 1991.

Gradient Corporation, 1994. Critique of the California Environmental Protection Agency "Health Risk Assessment for Diesel Exhaust". Cambridge, MA. September 2, 1994.

Gustafsson, L., S. Wall, L.G. Larsson, B. Skog, 1986. Mortality and cancer incidence among Swedish dock workers: A retrospective cohort study. *Scandinavian Journal of Work and Environmental Health*. 12:22-26.

Gustavsson, P., N. Plato, E.B. Lidstrom, C. Hogsted, 1990. Lung cancer and exposure to diesel exhaust among bus garage workers. *Scandinavian Journal of Work and Environmental Health*. 16:348-354.

Hayes, R.B., T.T. Silverman, D.T. Vineis, P. Blot, *et al.*, 1989. Lung cancer in motor exhaust-related occupations. *American Journal of Industrial Medicine*. 16, 685-695.

Heinrich, U., R. Fuhst, *et al.*, 1995. Chronic inhalation exposure of Wistar rats and two different strains of mice to diesel engine exhaust, carbon black, and titanium dioxide." *Inhalation Toxicology*, 7, 533-556.

Henderson, R.F., J.A. Pickrell, R.K. Jones, J.D. Sun, J.M. Benson, J.L. Mauderly, R.O. McClellan, 1988. Response of rodents to inhaled diluted diesel exhaust: Biochemical and cytological changes in bronchoalveolar lavage fluid and in lung tissue. *Fundamental and Applied Toxicology*, 11:546-567.

Jensen, F.V., 1996. *An Introduction to Bayesian Networks*. Springer-Verlag, New York.

Jenzerli, A., 1996. Solving influence diagrams using Gibbs sampling. Chapter 6 in D. Fisher and H-J Lenz (Eds), *Learning from Data: Artificial Intelligence and Statistics V*. Springer-Verlag, New York.

Judge, G.C., W.E. Griffiths, R.C. Hill, H. Lutkepohl, and T-C Lee, 1985. *The Theory and Practice of Econometrics: Second Edition*. Wiley, New York.

Kalbfleisch, J.D., and R.L. Prentice, 1980. *The Statistical Analysis of Failure Time Data*. Wiley, New York.

Kenny, D.A., 1979. *Correlation and Causality*. Wiley, New York.

Mauderly JL; Banas DA; Griffith WC; Hahn FF; Henderson RF; McClellan RO, 1996. Diesel exhaust is not a pulmonary carcinogen in CD-1 mice exposed under conditions carcinogenic to F344 rats. *Fundamental and Applied Toxicology*; 30 (2): 233-42

Mauderly, J.L., R.K. Jones, W.C. Griffith, R.F. Henderson, and R.O. McClellan, 1987. Diesel exhaust is a pulmonary carcinogen in rats exposed chronically by inhalation. *Fundamental and Applied Toxicology*, 9:208-221.

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

McCullagh, P., and J.A. Nelder, 1983. *Generalized Linear Models*. Chapman and Hall, New York.

Michie, D., D.J. Spiegelhalter, and C.C. Taylor (Eds.), 1994. *Machine Learning, Neural and Statistical Classification*. Ellis Horwood Series in Artificial Intelligence. Ellis Horwood, New York.

Milne, K.L., D.P. Sandler, R.B. Everson, S.M. Brown, 1983. Lung cancer and occupation in Alameda county: A death certificate case-control study. *American Journal of Industrial Medicine*. 4:565-575.

Muscat JE, 1996. Carcinogenic effects of diesel emissions and lung cancer: the epidemiologic evidence is not causal. *Journal of Clinical Epidemiology*; 49 (8): 891-2

Muscat, J.E. and E.L. Wynder, 1995. Diesel engine exhaust and lung cancer: An unproven association. *Environmental Health Perspectives*, 103(9), 812-818.

Nakamura, T., 1992. Proportional hazards model with covariates subject to measurement error. *Biometrics* 48, 829-638.

Nikula KJ; Snipes MB; Barr EB; Griffith WC; Henderson RF; Mauderly JL., 1996. Comparative pulmonary toxicities and carcinogenicities of chronically inhaled diesel exhaust and carbon black in F344 rats. *Fundamental and Applied Toxicology*; 25 (1): 80-94

Pearl, J., 1996. A causal calculus for statistical research. Chapter 3 in D. Fisher and H-J Lenz (Eds), *Learning from Data: Artificial Intelligence and Statistics V*. Springer-Verlag, New York.

Saari, D.G., 1987. The sources of some paradoxes from social choice theory and probability. *Journal of Economic Theory*, 41, 1-22.

Shafer, G., 1996. *The Art of Causal Conjecture*. MIT Press. Cambridge, MA.

Siegel, S., 1956. *Nonparametric Statistics*. McGraw-Hill, New York.

Sims, C.A., Multivariate time series models. In J. Eatwell, M. Milgate, and P. Newman (Eds.) *The New Palgrave Time Series and Statistics*. W.W. Norton and Company. New York, 1990.

Steenland, N.K., D.T. Silverman, and R.W. Hornung, 1990. Case-control study of lung cancer and truck driving in the Teamster's Union. *American Journal of Public Health*, 80(6):670-674.

Stober, W., and J.L. Mauderly, 1994. Model-inferred hypothesis of a critical dose for overload tumor induction by diesel soot and carbon black. *Inhalation Toxicology*, 6:427-457.

Valberg, P.A., and A.Y. Watson, 1996. Analysis of diesel-exhaust unit-risk estimates derived from animal bioassays. *Regulatory Toxicology and Pharmacology* 24: 30-44

Waller, R.E., 1981. Trends in lung cancer in London in relation to exposure to diesel fumes. *Environ Int.* 5:479-483.

Williams, R.R., N.L. Stegens, J.R. Goldsmith, 1977. Associations of cancer site and type with occupation and industry from the Third National Cancer Survey Interview. *Journal of the National Cancer Institute*. 59:1147-1185.

Wolff, R.K., R.F. Henderson, M.B. Snipes, W.C. Griffith, Jr., J.L. Mauderly, R.G. Cuddihy, R.O. McClellan, 1987. Alterations in particle accumulation and clearance in lungs of rats chronically exposed to diesel exhaust. *Fundamental and Applied Toxicology*, 9:154-166.

Wolff, R.K., W.C. Griffith, Jr., J.L., R.G. Cuddihy, M.B. Snipes, R.F. Henderson, J.L. Mauderly, R.O. McClellan, 1989. Modeling accumulations of particles in lung during chronic inhalation exposures that lead to impaired clearance. *Health Physics*, 57: Sup. 1, 61-68.

Wong, O., R.W. Morgan, L. Kheifets, S.R. Larson, M.D. Whorton, 1985. Mortality among members of a heavy construction equipment operators union with potential exposure to diesel exhaust emissions. *British Journal of Industrial Medicine*. 42:435-448.

Yao, Q. and D. Tritchler, 1996. Likelihood-based causal inference. Chapter 4 in D. Fisher and H-J Lenz (Eds), *Learning from Data: Artificial Intelligence and Statistics V*. Springer-Verlag, New York.

May 30, 1995

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My comments about the Health Assessment Document for Diesel Emissions are enclosed.

Chapter 2: Diesel Emissions

There seems to be an overlap between the content of Chapters 2 and 3. The aim of Chapter 2 is said "to present an accurate perspective on the diesel engine as a contributor to the mobile sources emissions inventory". However, elemental carbon as a marker of diesel exhaust emissions is discussed in Chapter 3. Depending on the reorganization of the document, some of my suggestions about Chapter 3 may be applicable to Chapter 2.

Work by Bradow from 1980 is quoted to indicate the atmospheric concentrations of fine particles attributable to diesel. There also is similar work by Cuddihy and coworkers from the same era that is not noted (Cuddihy et al, Potential health and environmental effects of light duties vehicles II, Albuquerque, 1981, Inhalation Toxicology Research Institute, Lovelace Biomedical and Environmental Research Institute). Cuddihy and coworkers provided estimates of ambient levels of diesel particles based on predictions of light duty diesel use did not materialize. It would be useful to note these predicted estimates of ambient diesel particle levels and compare them to levels predicted by measurements of elemental carbon measurements (see comments on Chapter 3) and levels predicted by EPA (US Environmental Protection Agency, 1993. Motor vehicle-related air toxics study. EPA/600/BP-92/003. Office of Research and Development, Washington, D.C.).

It would also be useful to present the effects of engine technology and control technology on diesel engine emissions. Particulate matter emissions for various diesel engine types have decreased since the 1970's. Such information is presented in the

report on diesel exhaust written by the Health Effects Institute. It is likely that lung cancer in workers with past occupational exposure to diesel exhaust occurred at higher levels when compared to current exposure.

Chapter 3: Diesel -Derived Pollutants: Atmospheric Concentrations, Transport, and Transformations

This chapter would be enhanced by a more detailed discussion of the contribution of diesel exhaust emissions to ambient concentrations of respirable particles and the current and future sources of these emissions. This would set the stage for the need to perform either a quantitative or qualitative risk assessment for diesel exhaust in the later chapters.

The contribution of diesel exhaust to respirable particles will vary based on proximity to traffic or other sources of diesel exhaust. As acknowledged in the chapter, the major difficulty in assessing the contribution of diesel exhaust to air quality has been the lack of a suitable marker for diesel exhaust. There is a detailed discussion of diesel exhaust associated organic compounds, but the use of elemental carbon as a marker of diesel exposure seems more promising. The use of elemental carbon for this purpose is mentioned briefly on page 3-57. Since this chapter was written, Zaebsst and coworkers (*Am. Ind. Hyg. J.* 52: 529-541, 1991) have published a study where they used a thermal-optical analysis to measure elemental carbon to estimate the diesel exhaust exposure of truck drivers. Sampling was done on major highways and in neighborhoods at least 1 mile from any major highway, and provides information on atmospheric concentrations of particles attributable to diesel. The study by Horvath et al. (1988) is also mentioned but deserves further discussion as one of the few studies that attempts to estimate the contribution of diesel vehicle emissions to air quality.

Cass and coworkers (*Atmos Environ* 18:153-162, 1984) and Gray (1986) have also reported on atmospheric concentrations of elemental carbon in the Los Angeles area. The study by Gray is briefly discussed on page 3-57 and dismissed as inadequate to be used to estimate ambient concentrations of diesel exhaust in an urban area. The study by Cass and workers is not included in the document. The authors of this chapter should reexamine the information found in these studies since it seems that elemental carbon is a reasonable marker for diesel emissions.

I realize that there may be some overlap with the PM10 document regarding the discussion of the contribution of diesel exhaust to ambient particle concentrations. This overlap can be minimized in this Health Assessment Document for Diesel Emission by limiting discussion to studies that contribute to estimates of the general population exposure to diesel exhaust particles.

A suggestion was made at the meeting to include a discussion

of off-road sources of diesel exhaust. Additional references that discuss current and future sources of diesel emissions (road and non-road sources) are:

1. Office of Air and Radiation, US Environmental Protection Agency: Non-road engine and vehicle emission study report, EPA 460/3-91-02 PB 92-126960, 1991
2. Association of American Railroads: Railroad facts, Washington, D.C., 1993.
3. American Automobile Manufacturers Association: World motor vehicle data, Detroit, 1993.
4. Office of Mobile Sources and Office of Air and Radiation, US Environmental Protection Agency: Regulatory impact analysis. Control of sulfur and aromatics contents of on-highway diesel fuel, Washington, DC, PB 93-207660, 1990.
5. Ward's Automotive Yearbook, Detroit, 1993, wards Communications.
6. US Department of Energy: Motor Fuel Consumption Model, Fourteenth Periodical Report, DOE/OR/21400-HL2, 1988.
7. American Public Transit Association: Transit fact book, p. 26, Washington, DC, 1992.

Chapter 5: Noncancer Health Effects of Diesel Exhaust

The precise definition of noncancer health effects should be discussed. In humans, this refers to acute effects due to odor, eye, and upper and lower respiratory tract irritation and possible chronic effects on symptoms and pulmonary function. In animals, additional morphologic information following high level exposure is available. This information is not available in humans.

The human noncancer studies are lumped together in 1 large table (Table 5-1). It is hard to put the information presented into context. The literature describing the human non-cancer respiratory health effects can be divided into 3 parts. First, there are studies of acute, short-term exposures; secondly, there are studies to examine cross-shift changes or short term occurrence of respiratory symptoms in occupational cohorts; and finally there are cross sectional studies and 1 longitudinal study that attempts to study the possible chronic effects of exposure. The table can be divided to reflect this. There then needs to be a summary of the studies described in each of these tables.

In the summary of studies of acute exposure it should be emphasized that in exposure studies (such as by Linnell and Scott

in 1962 and Battigelli in 1965) that there is variability in the diesel exhaust odor detection threshold. The studies describing an odor "scale" are studies where volunteers were exposed to diesel exhaust. The odor scales seem to have no general use at the present time. These studies can be quoted in qualitative rather than quantitative terms regarding variability in the ability to detect and rate the odor of diesel exhaust as objectionable. It can be emphasized that a great deal of what is known about acute exposure to diesel exhaust comes from case reports, such as by Kahn and coworkers in 1988. Cummins and coworkers (Br Med J 29:753-754, 1956) commented on a lacrimatory mist in a London bus garage when the buses were started in a cold morning. Wade and Newman (JOM 35: 149-154, 1993) describe 3 well-documented cases of reactive airways disease (that is not included in the document) following acute overexposure to locomotive exhaust.

Studies of the more subacute and shift related studies are those by Gamble et al. (Environ Res 42:201-214, 1987); Purdham et al. (Appl Ind Hyg 2:133-139, 1987); Ames et al. (Am Rev Respir Dis 125: 39-42, 1982); Ulfvarson et al. (Scand J Work Environ Health 13: 505-512, 1987); Ulfarson et al. (Am J Ind Med 17: 341-347, 1990); Ulfarson et al. (Am J Ind Med 19:283-289, 1991). The overall conclusion of these studies is that reversible changes in pulmonary function in humans can occur in relation to diesel exhaust exposure, although it is not possible to relate these changes to a specific level of exposure. Based on the case reports by Wade and Newman noted in the previous paragraph, reversible airflow obstruction and a syndrome consistent with asthma are possible following acute, high level exposure to diesel exhaust.

The studies attempting to study the more chronic respiratory effects of diesel exhaust exposure are those by Reger et al. (Ann Occup Hyg 26: 799-815, 1982); Attfield et al. (Ann Occup Hyg 26:817-831, 1982); Gamble et al. (Am J Ind Med 4:435-458, 1983); Gamble and Jones (Am Rev Respir Dis 128:389-394, 1983); Ames et al. (Arch Environ Health 39:389-394, 1984); Gamble et al. (Environ Res 44:6-17, 1987); and Attfield (1978). In these studies a relationship was generally observed between work in a diesel exposed job and respiratory symptoms (such as cough and phlegm) but there was no consistent effect on pulmonary function. The interpretation of these results are hampered by lack of actual diesel exhaust exposure levels and the short duration of exposure in these cohorts. Only active workers were included in these studies. It is possible that the relationship between work in a diesel exposed job and respiratory symptoms was due to short term exposure. On page 5-82 the statement is made that "most of the epidemiological data indicate an absence of an excess risk of chronic respiratory disease". Although this is qualified later on the next page, the major factor responsible is the lack of long term studies in diesel exposed workers.

There is one study which can be included in this chapter

where bronchoalveolar lavage was done after exposure to diesel exhaust. A slight increase in neutrophils was noted (Rudell B, Sandstrom T, Stjernberg N, Kolmodin-Hedman B. Controlled diesel exhaust exposure in an exposure chamber: pulmonary effects investigated with bronchoalveolar lavage. J. Aerosol Sci 21: S411-S414, 1990).

Chapter 8

Specific Comments

On page 8-1 there is a sentence discussing the transition from steam to diesel powered locomotives. It should be emphasized that this transition occurred mainly during the decade of the 1950's. In 1947, only 14% of the locomotives were diesel; by 1952 the number had risen to 55%, and by 1959, 95% of the locomotives were diesel (Woskie et al, Am J Ind Med 13:395-404, 1988).

The study by Gustafsson et al. (1986) was excluded from this chapter. This paper is a study of lung cancer mortality among dock workers between 1961 and 1980 exposed to diesel truck exhaust. An elevated SMR for lung cancer was found, and yearly lung cancer incidence rates increased at a rate greater than rates in Swedish males. This study also served as the basis of the case-control study by Emelin et al. (1993) which is discussed in the addendum to chapter 8. It would be appropriate to discuss these studies together.

On page 8-3 the comment is made that it is not clear whether the age range of the study by Waller (1981) included workers age 45 through 64 in 1950, 1964, or at the midpoint of the study. My interpretation of the study is that all men who age 45 through 64 at anytime between 1950 and 1964 were included.

The study by Howe et al. (1983) had some additional limitations that were not noted in the discussion. It is not clear which job titles were considered in the categories of nonexposed, possibly exposed, and probably exposed. Only retired workers were studied, so deaths among active workers presumably were not included. The active workers would have had the greatest potential exposure to diesel exhaust, and the true extent of diesel exposure experienced by these retired workers was not known.

The study by Boffetta and Stellman (1988) discussed on page 8-13 has 3 authors and should be referred to as Boffetta et al. (1988).

On page 8-18, the sentence starting with "directly standardized rate ratios...." on lines 13 through 15 is previously noted at the top of the page.

The study by Hall and Wynder (1984) discussed on pages 8-24

through 8-25 is a subset of the study later reported by Boffetta et al. (1990) discussed in the addendum to the chapter. It would be reasonable to discuss these studies together. It is worth noting the point estimate of the odds ratio for lung cancer of the effect of self reported exposure to diesel exhaust was 1.21, although significance was not achieved. This odds ratio is consistent with the results of other studies.

Since the publication of the paper by Steenland et al. (1990), an industrial hygiene survey by Zaebst was published as noted earlier, with further discussion relevant to lung cancer risk published by Steenland et al. in 1992 (Am J Indust Med 21:887-890, 1992).

The study by Gustavsson et al. (1990) is discussed in the addendum to chapter 8. There is comment that because the study has only 17 cases, the power of the study is small and misclassification of exposure would tend to bias the results toward unity. However, the study generally gave significant results.

General Comments

This chapter adequately presents the epidemiologic studies describing the relationship between diesel exhaust exposure and lung and bladder cancer. The discussion applying the Hill criteria of causality is reasonable. It would be helpful to the reader to present the results in graphical form presenting the odds ratios and 95% confidence limits. This would emphasize the similarity of the point estimates even if the point estimate were not statistically significant and emphasize the consistency of results in the literature. The point should also be made that in studies with an imprecise definition of exposure to diesel exhaust that includes potentially unexposed or individuals with little exposure, it would be more difficult to detect an effect of exposure and wide confidence intervals would result.

There is a section called relevant methodologic issues. These issues include the use of death certificates and next-of-kin smoking histories as a source of possible bias in the reporting of results. These same issues, particularly the use of death certificates are also noted in the discussion of each study and commented on each time. I think that the discussion of these methodologic issues can be noted here rather than repeated during the discussion of each study.

Another relevant methodologic issue is the assessment of the effect of smoking on lung cancer in the cohort studies of workers with diesel exposure but no direct smoking history. It might be worth stating that to be a confounder that the factor has to not only be associated with the outcome, lung cancer, but also the exposure. It can be said that when smoking was considered in the case-control studies that the odds ratios were of similar

magnitude to compared to studies where smoking information was not directly available. The Health Effects Institute Diesel Review presents these data in a concise format (see pages 269 and 270 in the review).

Another methodologic issue regarding the lung cancer studies in railroad workers regard exposure to pre-1959 combustion products. This is unlikely to significantly confound the results because the effect of work in a job working on and near operating trains was observed in the younger workers with more years of exposure to diesel exhaust compared to the older workers who would have worked during the steam era.

As stated in the Health Effects Institute Diesel Review, although the relative risks reported are modest, the elevations in lung cancer risk observed are unlikely to be explainable by confounding by smoking or any other cause of bias. However, I agree with the overall assessment using the regulatory jargon of "limited" evidence of carcinogenicity based on the human data linking lung cancer to diesel exhaust exposure. A limitation of the epidemiologic data is the crudeness of the exposure information. There is a lack of historic exposure data so that actual level of exposure can't be linked to cancer outcome. In addition, although the latency necessary for the occurrence of lung cancer has been generally met by these epidemiologic studies, there are no studies of lung cancer and in diesel exposed populations following many years (consistently greater than 20 to 30 years) of exposure. Completion of studies in different populations with well-characterized exposure over many years is a research need.

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

My comments on this chapter will be limited to the use of the human epidemiology data to produce an estimate of unit risk. There is a large body of human epidemiological studies indicating the relative of lung cancer attributable to diesel exposure is in the range of 1.2 to 1.5. EPA has supported an effort to obtain an estimate of unit risk using a data set developed by our laboratory. We agree with EPA that a major limitation in the use of this data set and others to conduct a risk assessment is the crudeness of the exposure data and the inability to determine how significantly exposures changed (decreased) over time. The relationship between cumulative exposure and lung cancer is dependent on modeling assumptions. This is obvious when the results obtained by the EPA supported effort are compared to the results obtained by the California Air Resources Board (sent to the Committee in a letter from Dr. Stanley V. Dawson). Our reanalysis of the data, documented in a letter to EPA in 1991, found a more uniform relationship with years of cumulative exposure and a non-significant relationship with various markers of cumulative exposure.

The solution to this problem is to obtain the "missing" deaths for the years 1977 through 1980 in the cohort, as well as additional years of follow-up. We have submitted a proposal to do this. However, it is possible that as a result of diminished exposure to diesel exhaust during the later years of the cohort that the relationship between calculated cumulative exposure and lung cancer will not monotonically increase. We believe that at this time, despite supporting the conclusion that the risk of lung cancer as a result of diesel exposure is increased, it is not possible to use the human epidemiologic data that was reanalyzed to assign a unit risk with confidence due to the uncertainty of the exposure data. If the calculation of unit risk is still desirable using this data set, it will be necessary to achieve a consensus of the scientists involved regarding all modelling assumptions.

Comments Of The Engine Manufacturers Association Regarding
The ARB/OEHHA Draft Report

"Proposed Identification Of Diesel Exhaust As A Toxic
Air Contaminant, February, 1998"

Dated: March 30, 1998

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Introduction

The Engine Manufacturers Association (EMA) hereby submits its comments and opposition to the ARB/OEHHA "Proposed Identification of Diesel Exhaust as a Toxic Air Contaminant (TAC)," which draft report is dated as of February 23, 1998 (the "Revised Draft Report").

EMA is the trade association that represents worldwide manufacturers of engines for all applications other than passenger cars and aircraft. Included among the many products manufactured by the more than 35 major corporations that comprise EMA's membership are a full array of diesel-fueled engines.

Through the efforts of EMA members, working in conjunction with federal and state agencies, including ARB, dramatic engine design improvements and emissions reductions have been obtained. An especially relevant example of these advancements is that emissions of particulate matter from diesel engines have been reduced by 90% over the past decade.

Given the substantial improvements that industry has made in emissions reductions through advanced engine technology and reformulated fuels, the assertions set forth in the Revised Draft Report regarding the alleged health effects of "diesel exhaust" remain matters of vital importance to EMA and its members. Indeed, the Revised Draft Report's assertions, as currently presented, could (for no sound scientific reason) spark public and private proceedings capable of threatening the viability of diesel power not only in the State of California, but nationally as well. Given the severe economic repercussions of such an outcome, it is

imperative that the Draft Report fairly address EMA's legitimate technical and scientific concerns so that the Report, when further revised, might present the "best available scientific evidence" and "sound scientific knowledge," as required by law. As it stands now, however, the Revised Draft does not do so, and so must be amended as detailed herein and in the appended supporting comments of EMA's consulting health research experts (Drs. Valberg, Cox and Vostal).

More specifically, the Revised Draft Report -- despite numerous prior comments and critiques from the leading scientists who have studied this subject -- continues to advance many unjustified and unbalanced findings and opinions, including the following:

- (1) The Revised Draft Report continues in its push to list whole "diesel exhaust" as a TAC, despite the fact that such a listing would be misguided and of no practical use to regulators or industry;
- (2) The Revised Draft Report continues to make sweeping statements about a supposedly "very likely" "causal" relationship between estimated diesel exhaust exposures and increased human carcinogenic effects, when no such causal relationship has been established;
- (3) The Revised Draft Report overstates and mischaracterizes the alleged bioavailability to humans of the organic compounds thought to be associated with diesel exhaust;
- (4) The Revised Draft Report does not address the critical issue of ambient "dose," which when properly considered with regard to biological thresholds establishes that increased health risks from ambient exposures to diesel exhaust are more than unlikely;
- (5) The Revised Draft Report fails to take into account the substantial reductions and changes in the characteristics of diesel exhaust emissions since the time of the postulated occupational exposures at issue in

the epidemiological studies upon which OEHHA relies to construct its conclusions;

(6) OEHHA's quantitative risk assessment based on epidemiological data, and as set forth in the Revised Draft Report, still utilizes non-standard and unjustified methods that many scientists do not support;

(7) The "body count" set forth in the revised Draft Report (e.g. ES-23, 1-16, 7-37) is completely inappropriate, fails to include "0" as a possibility, and lends a wholly unwarranted air of certainty to OEHHA's uncertain hypotheses and opinions that ambient exposures to diesel exhaust cause excess human lung cancers; and

(8) The manner in which the Revised Draft Report has been constructed and reviewed suggests that it has taken on the aspect of an adversarial position paper or manifesto against the use of diesel technology in the State of California, as opposed to a well-balanced and even-handed presentation of uncertain scientific issues.

In sum, EMA members are concerned that OEHHA is attempting to selectively construct a case against "diesel exhaust," rather than considering in an objective and even-handed manner the full body of evidence relating to the potential health effects that might or might not be associated with real-world ambient exposures to emissions from today's diesel engines. Selective arguments and opinions, however, are invalid substitutes for a balanced presentation of estimated risks based on sound scientific knowledge and correct technical methods. Indeed, as the Health Effects Institute (HEI) expressly admonished OEHHA in HEI's prior comments dated August 18, 1997, unbalanced presentation of uncertain issues "can undermine efforts to develop and communicate to the broader public an objective, thoughtful view of what the science is and is not telling us about the health effects of diesel exhaust."

Accordingly, unless and until the Revised Draft Report is

further revised to reflect an objective view of the science, the Report will remain inherently defective as an attempted justification for the proposed listing of "diesel exhaust" as a TAC.

1. **The Proposed Listing Of Whole "Diesel Exhaust" As A TAC Remains Misguided**

EMA has repeatedly stressed to ARB and OEHHA that the proposed TAC listing for whole "diesel exhaust" makes no sense. "Diesel exhaust" is 99.9% oxygen, water vapor, nitrogen and carbon dioxide. (IPCS Report No. 171, 1996, p. 101.) Indeed, even if diesel exhaust evolved to be 100% oxygen, nitrogen, water vapor and carbon dioxide (a goal which is being approached), it would still be "diesel exhaust," and so would still be "toxic" under the pending ARB/OEHHA proposal.

Moreover, what are regulators and industry to do to reduce "diesel exhaust" other than to ban or phase-out diesel engines? The posing of this question again highlights the fact that the Revised Draft Report reads like a manifesto or indictment against diesel engine technology as opposed to an instructive, informed and useful analysis of what, if any, specific components of diesel engine emissions should be targeted for further reductions in response to potential public health concerns. This is especially true given the fact that "diesel exhaust" is an ever-changing complex mixture, depending, in part, on engine type, fuel type, application and operating conditions. Thus, a listing of "diesel exhaust" necessarily will be so broad and unspecific as to be

effectively useless to those seeking to assess and possibly implement further specific emission control improvements.

To be of any utility, a TAC listing must identify the specific substance supposedly associated with an adverse health effect. Presumably, that is why there has never before been a TAC listing for such a broad, changing and complex mixture of numerous substances as contained within the rubric "diesel exhaust." No such overly-broad listing is justifiable in this context either.

In this context, just as in others, OEHHA needs to propose and justify a TAC listing of the specific constituent(s) of diesel exhaust that supposedly yield adverse public health outcomes, so that industry and regulators can strive to reduce emissions of those specific constituent(s). Since OEHHA has not done that, the pending TAC proposal in essence amounts to an initiative by the Agency to label a source of emissions -- diesel engines -- as a TAC, since that source is in effect the only real common denominator of OEHHA's intended listing of "diesel exhaust." But sources are not subject to TAC listings under the relevant statutes; specific "air pollutants" and "substances" are. That OEHHA would seek what amounts to a source listing targeting diesel engines again suggests that the Draft Report at issue is more a referendum than a health guidance document.

OEHHA's response to EMA's fundamental concern regarding the proposed TAC listing at issue is evasive to the point of being dismissive. More specifically, OEHHA has dismissed EMA's comments by stating that, "[t]he ARB is to respond to this inquiry." (Part

C, p. 59.) But ARB has claimed that the fashioning of the Revised Draft Report and the TAC proposal is OEHHA's responsibility. This failure to address such a basic and critical issue must stop. Indeed, OEHHA's seemingly arbitrary refusal to recognize or to respond to this point is indicative of an overall approach that OEHHA has exhibited in this process.

OEHHA's own document shows the weakness of its position on this point. OEHHA concedes that the particle fraction of diesel exhaust has been used as the basis for estimating exposure, and that the information that OEHHA reports concerning supposed genotoxicity was obtained from studies of diesel exhaust particles or extracts of diesel exhaust particles. More importantly, OEHHA further concedes at ES-19 that,

A general issue with regard to characterizing the toxicity of diesel exhaust is the variability of exhaust composition among types of engines and over different driving (or other use) conditions. However, findings suggest variability in toxicity may be small when the health evaluation is based on the concentration of particulate matter.

Moreover, in pursuing a listing for whole "diesel exhaust," OEHHA has failed to answer the question of why diesel exhaust deserves classification separate from other fossil-fuel and renewable bio-fuel combustion products. Within California, combustion soot from gasoline, heating oil, coal, charcoal, tobacco smoke, wood and cooking is ubiquitous. Unless and until OEHHA explains why the combustion product "diesel exhaust" is so markedly different from other combustion products, a TAC listing singling out "diesel exhaust" cannot be justified, and again indicates that

the Agency's goal is really a source (not substance) listing targeting diesel engines.

Such a source listing is not only procedurally defective, but scientifically unjustified as well. In that regard, OEHHA should fully and fairly inform the public of the true composition of the combustion products at issue to avoid what appears to be an effort by the Agency to foster unwarranted alarm regarding diesel exhaust. Thus, the Revised Draft Report should expressly note (as discussed in the comments of Dr. Valberg) that: (i) ambient concentrations of diesel exhaust (assessed through PM₁₀ measurements) are less than 1/25th of the current NAAQS for PM₁₀; (ii) diesel exhaust is 99.9% nitrogen, oxygen, carbon dioxide and water; (iii) the hydrocarbon fraction of diesel exhaust is only 7 parts per million of diesel exhaust; (iv) the PM fraction (even for pre-1991 diesel engines) is only 60 parts per million of diesel exhaust, and of that PM fraction the PAH content ranges from units to hundreds of parts per million; (v) overall, the PAH content of whole undiluted diesel exhaust is below 0.01 part per million; (vi) for the 1.5 ug/m³ diesel exhaust particulate concentrations to which Californians are exposed, the concentrations of PAHs are less than 0.0001 ug/m³; and (vii) for an individual breathing 20m³ per day, the daily PAH intake is approximately 0.002 ug/m³, an intake that is far below even typical background intake levels of PAHs which range from 2 to 20 ug/day. In fact, even if the total PAH intake is assumed to be bioavailable (an unjustifiably conservative assumption), the resulting unit risk value would be on the order of 2 x 10⁻⁶ based

on considerations of relative potency, significantly below the risks articulated by OEHHA in the Revised Draft Report.

In sum, the proposed TAC listing of whole "diesel exhaust" is in essence an invalid source listing, is not warranted based on the underlying studies of diesel particulate matter, is not practicable given the "variability of exhaust," is not justified when diesel exhaust is considered in conjunction with other combustion products and when the relevant composition and "dose" of diesel exhaust is fairly considered, and is completely misguided from a regulatory point of view. Consequently, this fundamental issue must be addressed before the Revised Draft Report advances any further in the TAC listing process.

2. **OEHHA's Opinions About "Causal" Relationships Do Not Fairly Represent The Data And Are Unjustified**

OEHHA's overall conclusions in the Revised Draft Report are that the epidemiological studies that OEHHA selected to rely on "provide evidence consistent with a causal relationship between occupational diesel exhaust exposure and lung cancer" (ES-20), that "at current ambient concentrations, diesel exhaust may cause an increase in the likelihood of cancer" (ES-26), and that "a reasonable and very likely explanation for the increased risks of lung cancer observed in the epidemiological studies is a causal association between diesel exhaust exposure and lung cancer" (6-59) (emphasis added). These conclusions are not well-founded in data and, when considered carefully, amount to OEHHA's unjustified opinion as opposed to sound scientific knowledge.

First, the fact remains that OEHHA has failed to apply any formal statistical tests for its asserted finding of a "very likely" causal association. Not a single statistical test of the hypothesis of causality has been performed or even cited.

Instead, in interpreting both rat and human data, OEHHA has used statistical models and methods that are biased to produce positive statistical associations between diesel exhaust exposure and lung cancer risk even in the absence of any true relation. OEHHA then subjectively interprets these associations as evidence of a causal relation, while carefully avoiding any statistical tests that could discredit such an interpretation. Moreover, and as detailed in the accompanying comments of Dr. Cox, OEHHA refuses to apply well developed and accepted statistical methods that would allow the Agency's assumptions about causality and risk to be tested objectively. The use of non-standard statistical tests wholly undermines OEHHA's interpretation that the perceived statistical associations are "very likely" causal.

Beyond the many methodological flaws inherent in OEHHA's analysis, the main substantive underpinning to its opinion about causation is the meta-analysis prepared by its staff. However, as Dr. Moolgavkar previously observed in his September 25, 1997 correspondence to OEHHA, "[n]o meta-analysis can correct for the deficiencies of individual studies, which remain a real concern with epidemiological studies of diesel exhaust." This is especially true in this case where the key epidemiological studies at issue lack any contemporaneous exposure data or

characterizations of the actual emissions from the sources of exposure. Indeed, as Dr. Debra Silverman of the National Cancer Institute (NCI) has stated, "[t]he repeated findings of small effects coupled with the absence of quantitative data on historical exposure, precludes a causal interpretation." (Epidemiology, Jan. 1998, Vol. 9, No. 1, p. 5.) (Emphasis added.)

OEHHA's assertions regarding a "very likely" causal relationship with "occupational diesel exhaust exposure" are therefore not well-founded in data. In fact, there is no actual occupational diesel exhaust exposure data for the studies on which OEHHA relies. Indeed, if OEHHA were to characterize the state of the science accurately, its Draft Report could only refer to a supposed association with "occupations/job categories deemed to have various estimated exposures to differing levels of emissions from 30-40 year-old diesel locomotive engines." Accurately describing what "exposure" was examined in the studies at issue readily identifies their limited relevance and utility.

Apart from OEHHA's overstatements concerning exposure, the causal conclusions/opinions that the Agency draws from its meta-analysis are directly contrary to the other independent meta-analyses conducted to date. For example, Stöber and Abel concluded in their 1996 report that "[t]here is no causal relationship between diesel exhaust inhalation and lung cancer" and that "there is certainly not any good evidence of a dose-response relationship" (p. S-41) (emphasis added). In their 1995 report, Muscat and Wynder stated that "[u]sing common criteria for determining causal

associations, the epidemiologic evidence is insufficient to establish diesel engine exhaust as a human lung carcinogen" (p. 812). See also L.A. Cox, Does Diesel Exhaust Cause Human Lung Cancer?, Risk Analysis, Vol. 17, No. 6, 1997. OEHHA fails to explain why these studies are dismissed.

Faced with substantial disagreement from multiple independent investigators to its conclusion of "very likely" causality, OEHHA now asserts that "another independently conducted meta-analysis of diesel exhaust exposure and lung cancer produced remarkably similar results [to OEHHA's]" (p. 6-49), and "found a similar consistency supportive of a causal relationship" (p. 6-52). OEHHA's description of this recently published analysis as "independently conducted" is, at best, a stretch, and at worst, intentionally misleading. The corresponding co-author of the Bhatia report, Dr. Allan Smith, is a co-author of OEHHA's Revised Draft Report. This might explain why the "independent" Bhatia report repeats so much material from OEHHA's report. This "independent" study was funded by the California EPA, and Dr. Smith may have participated in advance briefings and discussions concerning the report's conclusions. These circumstances suggest that the Bhatia study was not "independently conducted," and that OEHHA is attempting to generate newly-published documents to support its otherwise unsupported opinions. This type of practice, however else it might be described, is not sound science and greatly diminishes the credibility of the Revised Draft Report. Consequently, EMA requests that all references to the Bhatia analysis be stricken

from the Draft Report.

Perhaps even more remarkable than OEHHA's failure to disclose the close relationship between the authors of its report and the "independent" Bhatia study is that the Agency ignores truly independent reviews and critiques that were published at the same time. For example, in the same issue of Epidemiology where the Bhatia et al. analysis appeared, Dr. Silverman of NCI commented as follows:

Bhatia et al. conclude that the data support a causal association between diesel exhaust and lung cancer in humans. Has science proven causality beyond any reasonable doubt? Probably not. The repeated findings of small effects, coupled with the absence of quantitative data on historical exposure, precludes a causal interpretation. To establish causality will require well designed epidemiological studies that do not suffer from the weaknesses of previous studies.

(Epidemiology, Jan. 1998, Vol. 9, No. 1, p. 5.)

In ignoring these and other findings and opinions directly contrary to its position, OEHHA is acting in an arbitrary and capricious manner. Such arbitrary and one-sided reporting of the available data, however, cannot constitute sound science. Indeed, OEHHA's selective reporting of data concerning causation, coupled with its wholesale exclusion of contrary findings and opinions, can only serve to misinform policymakers, regulators and the public.

Other examples of OEHHA's selective analysis include its failure to discuss a 1997 review authored by Morgan, Reger and Tucker (published just weeks before the Bhatia report) (see Ann. Occup. Hyg., Vol. 41, No. 6, 1997, pp. 643-58). In this review,

Morgan et al. find that "[a]lthough there have been a number of papers suggesting that diesel fumes may act as a carcinogen, the weight of the evidence is against this hypothesis." (Emphasis added.) OEHHA again offers no explanation why the "independent" opinions of Bhatia et al. warrant OEHHA's enthusiastic endorsement, while the analyses of Morgan et al. and Dr. Silverman do not warrant discussion.

Further evidence of OEHHA's failure to adhere to the best scientific evidence has recently been uncovered. Previously, EMA had noted with concern that OEHHA's meta-analysis had "excluded from consideration studies focusing on mining occupations," even non-metal mining operations, with OEHHA claiming that "this was a conservative exclusion." (C-1.) What has emerged over the past few weeks, however, is that this "exclusion" may have been anything but conservative, and may instead have amounted to an unfair manipulation of the relevant data set.

More specifically, it has come to EMA's attention -- not through OEHHA or ARB -- that a report (a copy of which is attached) was published in 1997 (and also 1995) in the Australian and New Zealand Journal of Public Health (Vol. 21, No. 1) detailing an occupational study of nearly 24,000 coal miners in New South Wales over a 20-year period (1973-1992). This cohort study was designed to describe the incidence of cancer and was constructed from the medical examination records of the Joint Coal Board. Significantly, this large cohort study found no increased risk for lung cancer among the study population. To the contrary, the

reported SMR for lung cancer was 0.74 (CI = 0.50 to 1.06). See also The Medical Journal of Australia, Vol. 163, July 1995, pp. 19-21. The question then remains why these reports were excluded entirely from OEHHA's risk assessment while the supposedly "independent" work of Bhatia et al. was mentioned so prominently.

OEHHA's other efforts to justify its asserted finding of a "very likely" causal association also lack merit. More specifically, OEHHA's references (ES-21, ES-22) to the 1988 IARC listing of diesel exhaust as "probably carcinogenic" do not justify the causal conclusions set forth in the Revised Draft Report. As OEHHA well knows, the IARC listing was premised primarily on "sufficient evidence for the carcinogenicity in experimental animals of extracts of diesel engine exhaust particles." (See IPCS Report No. 171, p. 289.) As evidenced by the latest publications of Dr. Mauderly and others, however, current scientific understanding suggests that the animal data likely is not relevant to humans, a circumstance which calls the entire basis for IARC's listing into question.

Moreover, and contrary to OEHHA's suggestions (ES-22), the State of California engaged in no independent scientific investigation when it added diesel exhaust to the listing established under Proposition 65. Instead, the Proposition 65 listing was premised on the IARC listing, the validity of which (as noted above) is now in question. Indeed, members of the original IARC panel have stated recently that diesel exhaust would not be considered as a Group 2A carcinogen if reevaluated based on current

scientific understanding. In any event, the Proposition 65 listing does not constitute independent or separate scientific support for OEHHA's asserted conclusions regarding causal relationships.

Another point -- a point to which OEHHA also has not responded -- bears repeating. The claim for a causal role for diesel exhaust in the epidemiologic studies is severely undermined by the fact that the relative risks reported for lung cancer for a variety of occupations are remarkably similar, even though the estimated diesel exhaust exposures from occupation to occupation covered a three-order-of-magnitude range. As stated by Dr. Moolgavkar in his September 25, 1997 comments to OEHHA,

I also noted that some of the results of the meta-analyses were rather unexpected. For example, the level of risk in different occupational categories was rather similar, which is surprising in view of the different levels of exposure to diesel exhaust in different occupations.

More specifically, the summary meta-analysis value for all diesel exhaust epidemiologic studies is 1.33, with a range of 1.11 to 1.49 in the subanalysis by occupation. Even in the absence of actual exposure data, it seems implausible that, if diesel exhaust were causally increasing lung cancer risk by 40% for low exposure (e.g. truck drivers), the lung cancer risk derived for more heavily exposed worker populations (e.g. railroad workers and miners) would fall into the same estimated narrow range of small added risk.

For example, if diesel exhaust concentrations for truck drivers in the range of 10-20 ug/m³ produced a relative risk of 1.49 (the meta-analysis result), we can assign the 0.49 excess risk

to the 10-20 ug/m³ exposure. Consequently, diesel exhaust concentrations for underground miners in the range of 1000-2000 ug/m³ should have yielded excess risks 100 times larger than 0.49, or 49, meaning that the relative risk for diesel-exhaust-exposed underground miners would be expected to be 50 (1 + 49), whereas the actual reported relative risks range from 1.45 - 2.67 (0.74 for the Australian coal miners cohort). Such a complete lack of concordance strongly argues against a causal role for diesel exhaust in the reported epidemiologic associations.

Finally, OEHHA has attempted to bolster the significance of the weak associations reported for diesel exhaust by comparing them to associations of smoking with cardiovascular disease, for which OEHHA asserts relative risks ranging from 1.3 to 2.08. (C-19.) This argument is specious. A recent review of smoking data (Thun et al., 1997) has shown that the reported relative risks for coronary heart disease in smokers range up to 6.3 in men and 7.2 in women. Thus, OEHHA's claim that this widely recognized connection is based on "weak" and "very weak" epidemiological data is wrong. Moreover, the NCI itself has commented specifically on weak relative risks, stating

In epidemiological research, relative risks of less than 2 are considered small and are usually difficult to interpret. Such increases may be due to chance, statistical bias, or effects of confounding factors that are sometimes not evident. (NCI, 1994)

In sum, what HEI stated in 1995 still holds today. The results of the epidemiological studies -- which include at least ten studies with SMR's less than 1.0 (see Risk Analysis, Vol. 17,

No. 6, 1997, p. 812) -- exhibit a "weak association" between occupational exposure to diesel exhaust and lung cancer, but there is insufficient evidence to conclude whether confounding by other factors influenced the results. (HEI Report, p. 6.) Even OEHHA concedes that this "weak association" may "diminish the evidence for causality." (ES-20.)

That being the case, OEHHA cannot transform a weak association into a "very likely" causal relationship simply by stating that the epidemiological studies that it selected "provide evidence consistent with a causal relationship." (ES-20.) That statement is mere opinion, not well-founded in the available scientific data. Moreover, even that opinion is unwarranted since: (i) meta-analyses deal with statistical associations, not cause and effect; (ii) OEHHA has failed to perform any statistical tests for causality; (iii) the perceived "weak association" at issue can be explained by the multiple hypothesis testing or other artifacts that can be found in most of the epidemiological studies cited by OEHHA; (iv) OEHHA's opinion is premised on the "exclusion" of significant studies finding no increased risk and is contrary to other truly independent reviews and meta-analyses; and (v) there were no measurements or characterizations of actual occupational exposures in the studies relied on by OEHHA, so, at best, the perceived weak associations with increased risk are for job categories estimated to have varying potential exposures to diesel exhaust at differing levels decades ago.

The perceived "weak association" then cannot be deemed

"causal", and for OEHHA to do so is contrary to the weight of the evidence, evidence which OEHHA has reported in a highly selective and arbitrary manner. Thus, and as HEI wrote to OEHHA on August 18, 1997, OEHHA's opinions and assertions about causality "can undermine efforts to develop and communicate to the broader public an objective, thoughtful view of what the science is and is not telling us about the health effects of diesel exhaust."

For all of these reasons, therefore, OEHHA should delete its opinions and assertions of "very likely" causality, since they are unsupported by the weight of the scientific evidence, premised on unfairly selective data, and contradicted by the leading independent experts in the field.

3. **OEHHA's Conclusions About The Bioavailability Of The Organic Fraction Of Diesel Exhaust Particulate Matter Are Unbalanced, Overstated And Unjustified**

In its Revised Draft Report, OEHHA lists the few arguments in favor of bioavailability, but ignores all of the other evidence indicating that the organic fraction of diesel exhaust particulate matter may not be bioavailable to humans, especially at ambient concentrations. Indeed, none of the studies that OEHHA cites even pertains to assessments in human cell cultures of the supposed genotoxicity of whole diesel exhaust at ambient concentrations. Moreover, the genotoxicity of whole diesel exhaust has not been addressed in the animal studies performed to date. Thus, OEHHA's allegations regarding genotoxicity stem from diesel exhaust's postulated association with chemicals the genotoxicity of which have been cited in other contexts. However, neither the amount nor

the health consequences of those chemical compounds has been determined in the context of diesel exhaust.

By relying on particulate extracts as a surrogate of diesel exhaust, OEHHA incorrectly attributes a genotoxic role to exhaust or diesel particles without recognizing that the organic fraction must first be extracted by strong solvents and concentrated before any mutagenic action can be demonstrated. Moreover, laboratory studies have shown that particles dissociate much more slowly in vivo than when extracted by organic solvents in vitro, and that serum and tissue cytosols significantly reduced the cytotoxicity of diesel particulate extracts. As a result, and as detailed further in the comments of Dr. Vostal, mutagenic effects obtained through the testing of solvent extracts may well have falsely postulated effects that do not occur in living organisms.

OEHHA also fails to recognize that the direct application of unusually high concentration gradients does not replicate the actual contact of diesel particles with cells in the human body. Because most evidence of genotoxic action of whole diesel particles or exhaust have been obtained either by using concentrated solvent extracts of diesel particles or extremely high concentration gradients (mg mass per ml of media or tissue culture), OEHHA should recognize the obvious lack of relevance of these studies for actual conditions that are encountered in vivo after ambient exposures (i.e. 1.5 ug/m³).

Indeed, when the concentrations utilized in the studies at issue are recalculated in terms of lung surface distribution or

distribution in body fluid, it becomes clear that the studies involve completely unrealistic accumulations of particulate masses that simply are not present in actual environmental concentrations. More importantly, such extreme situations could never occur because before the supposed genotoxic effect of such exaggerated exposures could be manifested, the whole organism would suffer from the general toxicity of such extreme exposures. Consequently, and as also detailed by Dr. Vostal, OEHHA should critically evaluate the relevance of these findings before they are used in support of OEHHA's opinions concerning genotoxicity and bioavailability.

As a related point, OEHHA also equates genotoxic mechanisms of carcinogenicity with the absence of a threshold in the dose-response. That position fails to acknowledge what is currently known about DNA repair mechanisms. Because the dose to the respiratory tract of diesel particulate at ambient concentrations is so small, it is highly unlikely that DNA repair mechanisms would be overwhelmed. Thus, the possibility of a threshold must be considered among the possible mechanisms of human responses. Indeed, the extrapolation of any data to ambient exposures encountered by the California population must include the probability of a threshold, regardless of the proposed mechanism of action.

Further, OEHHA's conclusion about the presence of urinary PAHs from diesel exhaust exposure is not supported by the data and should not be used as evidence of bioavailability. Moreover, a simple quantitative calculation of the total quantity of PAHs that

are available from diesel exhaust levels at concentrations of 1.5ug/m³ show that the daily intake of PAHs is approximately 1000-fold below the baseline background intake of PAHs for the U.S. population.

OEHHA's assertion that DNA adducts have been associated with occupational exposure to diesel exhaust also is unjustified. Indeed, OEHHA has acknowledged that information on diesel exhaust exposure was not available for the studies at issue and that dermal exposures to diesel fuel and lubricating oil could have occurred. These and other extremely important caveats identified by Drs. Vostal and Valberg (such as food intake and smoking), which severely limit implicating diesel exhaust as the cause of DNA adducts, must be emphasized by OEHHA in any discussion of this point.

In sum, OEHHA's arbitrary and selective discussion fails to provide a balanced scientific review and account of the issues of genotoxicity and bioavailability. Indeed, as HEI has correctly noted, it is simply not clear what fraction of the genotoxic material associated with diesel exhaust is bioavailable, or whether the mutagenic potency demonstrated in vitro extends to the more complex in vivo environment. (HEI Report, p. 29.)

4. The Revised Draft Report Fails To Address The Critically Important Issue of Ambient Dose

Contrary to its conclusory assumptions regarding genotoxicity and bioavailability, OEHHA's emphasis should be on whether a toxic dose of diesel exhaust can be found in the environment at ambient

concentrations. The dose of deposited particulate in the lung from an exposure concentration of $1.5\mu\text{g}/\text{m}^3$ is extremely tiny. Indeed, the daily deposited dose is less than 1 particle per 100 alveoli or less than 1 particle per 600 alveolar macrophages. This level of particle deposition will be readily ingested by macrophages, with the particles isolated within phagolysosomes.

Consideration of the systematic dose from this low level of airborne particulate suggests that the daily dose is below "no effect" levels. Indeed, the daily dose of pure arsenic judged to be without adverse health effects is 14-fold larger than the dose of diesel exhaust at issue, while the dose of cyanide judged to be without adverse health effects is 1000 times larger. OEHHA needs to provide comparisons of this kind so that policymakers and the public can put OEHHA's assertions about diesel exhaust into better perspective.

Moreover, a comparison of the "mutagenic dose" of the diesel exhaust organics, even if completely bioavailable (which they are not), shows that the quantitative dose is again exceedingly small. A comparative potency analysis shows that, assuming the mutagenic activity of diesel engine exhaust is 100% bioavailable, current diesel exhaust levels in California result in an estimated risk equivalent to smoking one cigarette every 6 to 16 years. This would be equivalent to a person smoking three to eight cigarettes over a 70 year lifetime, starting at age 20, which according to the comments of several of the leading scientists in this area corresponds to a unit risk on the order of 2×10^{-6} . In order, for

OEHHA to correctly communicate the spectrum of truly small risks attributable to diesel engine exhaust, it is essential to provide such perspective in the Revised Draft Report. Indeed, OEHHA's assertions of "very likely" causal associations without having sufficiently established the critical criterion of biologic plausibility are scientifically unjustified. See Weed and Hursting, Amer. J. of Epid., Vol. 147, No. 5, 1998.

5. The OEHHA Draft Fails To Account For The Use Of New Engine Technology And Reformulated Fuels In California

OEHHA concedes that "a general issue with regard to characterizing the toxicity of diesel exhaust is the variability of exhaust composition among types of engines and over different driving (or other use) conditions." (ES-19.) OEHHA nevertheless skips over this conundrum by focussing on the toxicity of particulate matter emissions, while simultaneously maintaining a proposed listing for whole diesel exhaust. Despite OEHHA's unscientific gyrations in an apparent attempt to play both sides of the street on this issue, what OEHHA utterly fails to account for is the advent of new engine technology and low-sulfur, low-aromatic diesel fuels. This is more than a little significant. In fact, the emissions from today's engines running on today's fuels are dramatically different from the estimated emissions to which railroad workers may have been exposed back in the 1960's and 1970's.

The proof of this point is clear and is in the hands of the State of California. More specifically, on or about January 30,

1998, the California EPA released a draft report prepared under contract by the College of Engineering - Center for Environmental Research and Technology (CE-CERT) of UC Riverside, entitled "Evaluation of Factors that Affect Diesel Exhaust Toxicity" (hereinafter, the "CE-CERT Report"). This CE-CERT Report details certain of the air quality (and public health) benefits resulting from the use of post-1993 diesel fuels. EMA questions why OEHHA has elected not to discuss this CE-CERT Report data given the critical importance of this issue.

The data in the CE-CERT Report are very significant and indicate that the potential toxic compounds contained in diesel exhaust are becoming much smaller contributors to overall emissions through the use of new fuels, even before factoring in the benefits derived from the use of current engine technologies. More specifically, and as evidenced in part by Figure 27 of the CE-CERT Report (p. 139), emissions of total mutagenic compounds have been reduced by 50%-60% through the now-mandated use of low aromatic fuels. Bioassays conducted by CE-CERT have confirmed that emissions from engines running on reformulated fuels exhibited lower mutagenic activity. (CE-CERT Report, p. 176.) In addition, emission rates of particulate matter have been reduced by up to 25% compared to pre-1993 fuels (CE-CERT Report, p. 170), while emission rates for volatile organic compounds have been reduced by similar amounts.

Other specific findings from the CE-CERT data bear special note. For example, nitroaromatic compounds have been identified in

diesel particle extracts as the chemical agent responsible for the mutagenic effects in Salmonella bioassays conducted in the late 1970's and early 1980's. Using sensitive Thermosorb cartridges, data from the CE-CERT project show, however, that N-nitrosomethylamine and N-nitrosodipropylamine are detected in today's diesel exhaust only at levels that are close to their detection limits. Further, reformulated fuel emissions yield levels that are non-detectable (no other nitrosamines including nitrosomorpholine were detected).

These findings clearly call into question the relevance of prior epidemiological studies of estimated occupational exposures to locomotive engine emissions that may have occurred 30-40 years ago, especially since those studies included no contemporaneous exposure data whatsoever. These findings also severely undermine OEHHA's opinions regarding genotoxicity, bioavailability and causality. Indeed, OEHHA's failure even to mention, let alone address, the significance of the CE-CERT Report is again suggestive of an arbitrary and unbalanced reporting of the available evidence. Regardless of the motive behind OEHHA's selective reporting, the data compiled in the CE-CERT Report provide additional support for the fact that OEHHA's opinions do not reflect (and are in fact contrary to) the best available scientific evidence.

6. OEHHA's Quantitative Risk Assessment Is Not Justified

EMA has repeatedly stated its strong opposition to the quantitative risk assessment that OEHHA has constructed based on

the Garshick et al. studies of railroad workers. EMA renews its objections here.

As OEHHA well knows, Dr. Garshick himself has stated in correspondence to the Agency dated August 11, 1997, as follows:

I do not believe that your current document fully expresses the uncertainty of the estimates of risk that you have presented [I]t is not possible to use a positive slope to definitely describe the relationship between cumulative exposure and lung cancer mortality. I believe that the use of a slope as derived in the OEHHA assessment has not been justified.

OEHHA's response to Dr. Garshick's fundamental concerns has been, in effect, to multiply (not correct) the fundamental concerns. Instead of abandoning a quantitative risk assessment based on inappropriate data (which included no actual exposure measurements or information about the emissions characteristics of the exposure source), OEHHA has elected to multiply the number of unit risk calculations derived from the data, as though constructing more unit risk factors from the same inappropriate data will lend credence to the exercise. It does not. Multiple iterations and sensitivity analyses of unjustified calculations do not address the problem (i.e. that the Garshick data does not allow the calculation of unit risks with confidence); such iterations (not surprisingly) simply compound the problem. Indeed, OEHHA seemingly would prefer that the readers of its Report be overwhelmed by more and more inappropriate calculations, rather than concede that its calculations cannot be justified given the present state of the available epidemiological data. This is all

the more remarkable since OEHHA itself has conceded that the Garshick studies exhibit only an "apparent finding of a relationship of cancer rate to duration of exposure." (ES-23.)

EMA is not alone in the view that OEHHA's quantitative risk assessment lacks adequate scientific basis. HEI has stated unequivocally that "the lack of definitive exposure data for the occupationally exposed study populations precludes [not "limits" as OEHHA represents (ES-22)] using the available epidemiological data to develop quantitative estimates of cancer risk." (HEI Report, p. 8.) Similarly, WHO's 1996 report declares in unequivocal terms that "[a] quantitative risk assessment cannot be conducted on the basis of epidemiological data in which job title was used as a surrogate of exposure Consequently, there are no human data suitable for estimating unit risk." (IPCS Report No. 171, p. 254.)

Further, OEHHA's quantitative risk assessment fails to account for the myriad uncertainties inherent in rendering such a calculation. This too undermines the validity of the attempted calculation. OEHHA's listing of uncertainties is simply not the same as accounting for them in the relevant calculations. The result is that OEHHA's reported range of quantitative risk estimates as well as its stated confidence intervals do not adequately account for the uncertainties at issue, including misclassification errors, exposure estimation errors, errors in controlling for background, errors in controlling for smoking and other confounders, the probability of non-linear response, errors

in slope estimates, and other modeling and methodological errors.

In sum, OEHHA continues to proceed in a non-standard manner inconsistent with the weight of scientific evidence. As a result, OEHHA's quantitative risk assessments -- multiplied as they may have become -- remain invalid.

At the very least, if OEHHA insists on maintaining its non-standard methodology and approach to its risk assessment, the range of risks reported (see, e.g., Table 1-1 at ES-24) must be amended to include a unit risk of "0." Inclusion of "0" is necessary to account for: (i) the independent meta-analyses that found no causal relationship between estimated occupational exposures to diesel exhaust and increased risks of lung cancer; (ii) the negative epidemiological studies that OEHHA either excluded or ignored;¹ (iii) OEHHA's failure to conduct any statistical tests of causality; (iv) the probability that the organic fraction of diesel exhaust particulate matter is not bioavailable; (v) the dramatically reduced levels of emissions of mutagenic compounds from today's engines running on today's fuels; (vi) the low ambient levels of diesel exhaust to which people are exposed in the real world; (vii) the probability that any potential carcinogenic response is non-linear and may in fact exhibit a threshold; and

¹Contrary to OEHHA's apparent dismissal of negative studies, the supposed "healthy worker effect" is not an effective rebuttal to a finding of no increased relative risk where cancer is the relevant health end-point at issue. Given the various potential mechanisms postulated for human carcinogenesis -- including genotoxic mechanisms -- a "healthy worker" would not necessarily be possessed of any unique immunities. Consequently, OEHHA's apparent wholesale dismissal of negative studies is not justified.

(viii) the overall uncertainty of OEHHA's entire exercise in manufacturing a quantitative risk assessment.

7. OEHHA's Inclusion Of A "Body Count" In Its Report Is Unwarranted And Not Justified By The Best Scientific Evidence

In its Revised Draft Report, OEHHA estimates that as a result of exposures to ambient levels of diesel exhaust there will be "200 to 2000 additional cancer cases for every one million Californians over a 70 year lifetime." (ES-23.) OEHHA has conceded previously that this "body count" is not a required component of its risk assessment process, which suggests that the "body count" (which fails to include "0" as a probable number) is a wholly unnecessary (if not inflammatory) rhetorical assertion that will only serve to foster unwarranted efforts to ban the use of diesel engines in California. Why else would OEHHA feature this unnecessary quantification of death, a quantification that necessarily will alarm the public and provide tidy sound bytes for the media. (See, e.g. WSJ, 12/24/97, p. CA1; WSJ, 3/18/98, p. CA4.)

Moreover, the "body count" clearly lends a wholly inappropriate and misleading sense of certainty to the existence and magnitude of a cause and effect relationship in an otherwise wildly uncertain quantitative risk assessment. This exercise in body counts then is not sound science, but advocacy. Given the "considerable uncertainty" (ES-25) at issue, therefore, OEHHA's unnecessary and unjustified body count should be dropped, or at the very least amended to include "0" as a reasonable estimate.

8. **The Manner In Which The Revised Draft Report Has Been Developed Is Inconsistent With Due Process**

EMA and its consulting experts have expended significant efforts over many years in reviewing the critically important health effects issues that potentially relate to emissions from diesel engines. As part of these efforts, EMA and its consulting experts have submitted detailed comments on each draft of the OEHHA Report. EMA members also have provided OEHHA staff with numerous additional data, reports and analyses in the hope that OEHHA would conform its document to the best available scientific evidence.

Unfortunately, and as evidenced by the Revised Draft Report (including Part C), OEHHA has elected to treat EMA's comments as mere debating points, worthy only of recharacterization, rebuttal and dismissal. OEHHA's adversarial practice in this regard does a disservice to the iterative process that ought to determine whether and on what basis a TAC listing might be warranted. The comments of EMA and its consultants are based on sound scientific data and analyses and have been submitted so that the Draft Report might incorporate and reflect that data and analyses. Those comments then have been submitted for inclusion in the Report, not exclusion through OEHHA's utilization of selective rebuttal points and one-sided argument. Consequently, EMA urges OEHHA to act with due regard to the pending process and include the substance of EMA's comments in the findings and conclusions of the Draft Report. Only through such incorporation will the Draft Report be able to reflect an even-handed and careful approach to the uncertain health effects

issues with which we are concerned.

EMA also has recently become aware of several factors suggesting that OEHHA, be it intentional or not, has selectively reported data in a manner suggesting unfair bias. Indeed, as noted previously, the OEHHA report reads in many respects like a one-sided position paper or manifesto against the continued use of diesel technology in the State of California. While a ban on diesel technology may be the goal of some representatives of ARB/OEHHA, that objective simply does not follow from the best available scientific evidence, especially if that evidence is reported in an even-handed manner without exclusions. Moreover, that goal may be doubly imprudent in light of increasing concerns regarding "greenhouse gases," which are emitted from diesel engines in very low amounts when assessed against other potential power sources.

Given recent developments, therefore, and in addition to requesting specific responses from OEHHA to all of the comments submitted herewith, EMA seeks answers from OEHHA to the following questions regarding the preparation of the Revised Draft Report:

i. What is the justification for OEHHA's highlighting of the Bhatia et al. report as an "independently conducted" meta-analysis, inasmuch as an author of the Revised Draft Report was a co-author of the meta-analysis, which was funded by California EPA and pre-discussed with OEHHA?

ii. Why do the meta-analyses of Stöber and Able, Muscat and Wynder, and Morgan, Reger and Tucker, as well as the article by Dr. Silverman, receive such short shrift in the Revised Draft Report?

iii. Why was the cohort study of coal miners in New South Wales excluded entirely from the OEHHA report?

iv. Why are the implications from the extensive data contained in the CE-CERT Report not even mentioned in the Revised Draft Report?

v. Why is "0" not included within the range of risks and UCLs reported by OEHHA, since, among other things, at least three statistically significant epidemiological studies found the relative risk for lung cancer to be less than 1.0, causality has not been adequately established, current emissions data have not been accounted for, biologic plausibility based on ambient doses has not been demonstrated, the probability of a threshold response cannot be excluded, and the entire quantitative risk assessment process in this case is inherently uncertain and subject to dispute?

vi. Why is a body count (which does not include "0" as the low end of the range) included in the Revised Draft Report?

vii. To what extent have members of the Scientific Review Panel become contributing authors of the Revised Draft Report as opposed to "independent" peer reviewers (see, e.g., Transcript of 10/16/97 SRP Meeting, pp. 75, 112-114 and 119-121)?

viii. How did the reported range of risks change in response to the prior comments of EMA and its consulting experts?

Conclusion

The Revised Draft Report remains deficient in many fundamental areas, and (after all this time and effort) still reads like a position paper against diesel technology rather than an objective, even-handed presentation of what the available science does and does not tell us about the health effects of diesel exhaust. Consequently, the Revised Draft Report must be amended as indicated herein and in the appended expert reports of Drs. Valberg, Cox and Vostal to meet even the most minimal standards for sound science.

In that regard, the words of Dr. Silverman of NCI bear repeating:

Has science proven causality beyond any reasonable doubt? Probably not. The repeated findings of small effects, coupled with the absence of quantitative data on historical exposure, precludes a causal interpretation. To establish causality will require well designed epidemiological studies that do not suffer from the weaknesses of previous studies.

. . . . The scientific community has a responsibility to continue to pursue the question of whether diesel exhaust is a human carcinogen, a task beyond the limits of a meta-analysis of existing studies.

EMA is committed to pursuing new, well-designed epidemiological studies to further our understanding of these important issues and has committed its financial resources to such efforts. Pending the results of those efforts, however, the conclusions postulated by OEHHA remain unjustified by the best available scientific data. EMA therefore encourages ARB and OEHHA to assist in the procurement of new data and to curtail the misapplication of old studies that necessarily will remain scientifically insufficient for either causal conclusions or attempted quantifications of otherwise weak associations.

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The occurrence of cancer in a cohort of New South Wales coal miners

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Abstract To describe the incidence of cancer in coal miners in New South Wales (NSW) between 1973 and 1992, an inception cohort of all male coal industry employees who entered the industry between 1 January 1973 and 31 December 1992 was constructed from the medical examination records of the Joint Coal Board. This cohort was matched with the NSW State Cancer Registry to determine the occurrence and type of cancer. In the cohort of 25 630 men, 297 developed 301 primary cancers in the 20-year period of observation. The standardised incidence ratio (SIR) for all cancers was 0.82. Stomach cancer has been reported to be common in coal miners but the SIR for stomach cancer was not higher than average in this cohort. A cluster of non-Hodgkin's lymphoma has been reported in a NSW coal mine but an increased risk of this cancer was not evident in the industry as a whole. Similarly a cluster of cases of brain tumour has been reported. In this cohort, the SIR for brain tumour was 1.05 (95 per cent confidence interval (CI) 0.57 to 1.76) and a risk for brain tumour remains unconfirmed. The SIR for malignant melanoma was 1.18 (CI 0.90 to 1.90) altogether and 2.02 (CI 1.51 to 2.98) for those workers who started in an open-cut mine. Overall, there does not appear to be a general risk of cancer in the NSW coal industry. Open-cut miners have an increased risk of malignant melanoma, which may be related to their exposure to the sun at work. (*Aust N Z J Public Health* 1997; 21: 29-32)

THE history of coal mining is littered with cave-ins and explosions—ample evidence that this is a dangerous industry. Accidents and injuries have always been prominent,^{1,2} and if this were not enough, lung disease, specifically coal workers pneumoconiosis, has been the traditional occupational disease.³ Conditions have improved over the years. Control of dust in mines and regular medical surveillance have led to a dramatic reduction in lung disease in coal miners; the mortality from respiratory disease among New South Wales (NSW) coal miners is now similar to that of the general community.⁴ The mortality of NSW coal miners has recently been found to be less than that of the general population, reflecting a 'healthy worker effect', but there remains an excess of deaths from accidents.⁵ While the introduction of safe mining practices has reduced the risk of accident and dust diseases, other hazards to the miner may be emerging. Cancer has been suggested as a risk of coal mining and there

have been reports of clusters of cancers in various NSW coal mines.^{6,7} The occurrence of these clusters of cancer has raised concern about cancer in the coal industry generally.

In NSW, coal production traditionally has been one of our most important industries, both as an employer and as a major export earner. Coal miners, possibly uniquely among Australian industrial workforces, are represented on a database, which has been developed over many years by the Joint Coal Board. The NSW Central Cancer Registry has been population-based since 1972, and reliable data from the beginning of 1973 are available for matching. It was possible to analyse an inception cohort for the occurrence of cancer in those employees of the NSW coal industry who entered the workforce from January 1973 to December 1992.

Methods

Since the late 1940s the Joint Coal Board has had a program of medical examinations for workers entering the industry and periodically thereafter. The entry examination has been almost universal, so the list of people who have ever had one should include

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all those who have worked in the NSW coal industry since the Joint Coal Board commenced operation. The Joint Coal Board has had computerised records since the early 1970s.

From these records, we assembled an inception cohort consisting of all male coal industry workers who were first registered with the Joint Coal Board on or after 1 January 1973, or were recorded as having had their first Joint Coal Board medical examination on or after 1 January 1973 and before the end of the follow-up period. The date of entry to the cohort was taken as the first of these two dates, and only those men who were 60 years of age or under on 1 January 1973 were eligible. The start date of 1973 was chosen because from this date information on the incidence of cancer was available from the NSW Central Cancer Registry and because mining practices from that time are relevant to current conditions.

The cohort was followed until 31 December 1992. The coal industry employs a small number of women, mostly in office positions (although this is changing); however, there were too few women (406) for meaningful analysis. The cohort consisted only of men, and the final membership was 28 630.

We matched the data file from the Joint Coal Board with data from the NSW Central Cancer Registry, using the computer program Automatch,⁸ to identify members of the cohort who had developed cancer. The completeness of the Cancer Registry is good, and its reliability has been accepted by the International Agency for Research on Cancer.⁹ Initial matching results were verified by referring to the paper records of the Joint Coal Board and the Cancer Registry.

For this study, 'occurrence of a cancer' was defined as the first appearance on the NSW Central Cancer Registry of the name of a member of the inception cohort. Men who had had a cancer registered before they started in the industry were excluded as new cases of cancer, unless they developed another cancer. Skin cancers, apart from melanoma, and benign tumours are not recorded on the register and therefore cannot be included in the cohort's cancer experience.

Complete occupational histories were not available from the database. It was not possible to identify for certain that a man had left the coal industry or to determine his length of time in the industry. The most available and reliable data concerned the employment location at the time of first contact with the Joint Coal Board. Each person was therefore classified by his job location at the time of entry to the cohort. Some men examined by the Joint Coal Board did not work in coal a mine because they did not pass the medical examination, had the examination in the hope of employment that did not evenuate or worked for another company (such as a transport or maintenance company) that used the Joint Coal Board for medical services. Men who started in a coal mine were classified by their 'mine of start' being underground or open-cut but the 'mine of start' might not have been the mine in which they spent most time or have been the mine

of last employment. Nevertheless, industry and union representatives confirmed that over the period studied, movement of a miner from open-cut to underground work was unusual. For this reason, occurrence of cancer in men who worked in open-cut mines and those who worked underground can be compared. Movement of people from one type of mine to the other would tend to dilute any differences. Comparisons of one underground mine and another, or one open-cut mine and another would not be valid.

The data were analysed using SAS.¹⁰ For indirect age-standardisation, expected cancers were calculated from the Cancer Registry's cancer incidence rates for all of NSW from 1973 to 1992. Standardised incidence ratios (SIRs) were calculated and 95 per cent confidence intervals (CIs) for SIRs were calculated, assuming a Poisson distribution and using a method described by Morris and Gardner.¹¹

Table 1: Age-standardised cancer incidence ratios (SIRs) in a cohort of New South Wales coal miners

Cancer or site	Incidence		SIR	CI ^b
	Observed	Expected		
All cancers	302	346.25	0.82	0.73 to 0.92
Lip	10	9.85	1.02	0.49 to 1.87
Other mouth and pharynx	8	14.3	0.49	0.21 to 0.97
Stomach	7	10.01	0.70	0.29 to 1.44
Colon	27	27.04	1.00	0.66 to 1.45
Rectum	15	18.13	0.83	0.46 to 1.36
Other gastro-intestinal	9	14.71	0.67	0.26 to 1.09
Larynx	4	8.9	0.62	0.37 to 2.21
Lung	29	39.16	0.74	0.60 to 1.00
Pancre	2	1.9	1.05	— ^c
Nasal cavities, sinuses	1	1.85	0.54	— ^c
Teste	4	2.4	1.67	— ^c
Connective tissue	3	5.92	0.51	— ^c
Melanoma	85	75.52	1.13	0.90 to 1.39
Prostate	6	12.91	0.43	0.16 to 0.96
Teste	21	22.18	0.95	0.69 to 1.45
Bladder	10	12.45	0.80	0.39 to 1.48
Brain and other nervous system	14	13.36	1.05	0.57 to 1.76
Lymphomas, etc.	18	29.91	0.62	0.37 to 0.98
Multiple myeloma	1	3.59	0.28	— ^c
Leukaemia	5	11.96	0.42	0.14 to 0.98
Other cancers	21	22.6	0.98	0.68 to 1.43

Notes:

- (a) SIR = incidence ratio indirectly standardised, based on specific incidence of cancer in males in New South Wales, 1972 to 1991.
- (b) CI = 95% confidence interval, assuming Poisson distribution.
- (c) Where the observed number of cancers was less than 2, the 95% confidence interval was not calculated because the numbers were too small for a meaningful result.

CANCER IN COAL MINERS

Results

The average age of men in the cohort at the end of the follow-up period was between 40 and 50 years, and although there were many older men who were born before 1944, essentially this was a young cohort. Most men (75.8 per cent) were employed in a colliery at the time they joined the industry, 13.9 per cent were in the coal industry but not working in a mine, 7.3 per cent were not in the industry and 2.5 per cent could not be classified.

A total of 297 men were identified as appearing on the Cancer Registry between the beginning of 1978 and the end of 1993. Of these, five people appeared twice, that is, they developed a second primary cancer. The total number of cancers was 302.

The SIRs for all cancers and site-specific cancers are given in Table 1. The SIR for 'all cancers' was 80 per cent lower than expected from the rates applying in the reference population (NSW). Rates for cancer of the stomach and lung cancer were not higher than expected. Both have been reported in association with coal mining.

Cancers of the brain and nervous system, lip, colon and larynx had SIRs of 1 or slightly more, but the confidence intervals were wide and included 1. Similarly, while the SIRs for cancers of the pleura and bone exceeded 1, the numbers of cases were so low that meaningful confidence limits could not be calculated.

There were 25 cases of melanoma (with 75.5 expected). The SIR was 1.13, but the confidence interval included 1.

To explore possible mine-related factors, further analysis was restricted to those men recorded as starting work in a coal mine. Again, the SIR for all cancers was not significantly high and there was no appreciable difference in cancer occurrence between those starting in underground and those starting in open-cut mines (Table 2).

Three specific cancer groups (lymphoma, brain tumour and melanoma) were considered further. Lymphoma and Hodgkin's disease were the subject of the Hunday Colliery cancer cluster.⁶ A cluster of brain tumours from a NSW mine has been reported.⁷ It has been suggested that melanoma may be more common in those working in coal mines.¹²

Table 2: Age-standardized cancer incidence ratios (SIRs) in a cohort of New South Wales coal miners, by type of mine of start

Type of mine	Incidence		SIR*	CI ^b
	Observed	Expected		
Underground	178	209.57	0.85	0.73 to 0.98
Open cut	56	84.79	0.99	0.74 to 1.94
All coal mines	234	244.36	0.96	0.77 to 0.99

Notes:
 (a) SIR = incidence ratio indirectly standardized, based on specific incidence of cancer in males in New South Wales, 1972 to 1991.
 (b) CI = 95% confidence interval, assuming Poisson distribution.¹¹

Table 3: Age-standardized incidence ratios (SIRs) for selected cancers in a cohort of New South Wales coal miners, by type of mine of start

Type of cancer and type of mine	Incidence		SIR*	CI ^b
	Observed	Expected		
Lymphoma and Hodgkin's disease				
Underground	13	17.99	0.73	0.40 to 1.28
Open cut	1	4.71	0.21	— ^c
All mines	14	22.10	0.63	0.35 to 1.06
Brain tumour				
Underground	11	8.03	1.37	0.68 to 2.68
Open cut	0	2.11	—	— ^c
All mines	11	10.14	1.08	0.54 to 1.94
Melanoma				
Underground	44	48.32	0.97	0.71 to 1.30
Open cut	25	12.37	2.02 ^d	1.31 to 2.98
All mines	69	57.69	1.20	0.99 to 1.51

Notes:
 (a) SIR = incidence ratio indirectly standardized, based on specific incidence of cancer in males in New South Wales, 1972 to 1991.
 (b) CI = 95% confidence interval, assuming Poisson distribution.¹¹
 (c) Where the observed number of cancers was less than 5, the 95% confidence interval was not calculated because the numbers were too small for a meaningful result.
 (d) $p < 0.05$

In this study, melanoma had an elevated SIR and a large number of cases. Table 3 shows the SIRs for these cancers for the group that started in a coal mine. The SIR for lymphoma and Hodgkin's disease was not elevated overall, nor was it elevated for those working in either of the mine types. For brain tumours, the SIR for all mines was marginally elevated, with all the cases occurring in underground miners. As a consequence, the SIR for the underground miners was 1.37, but with only 11 cases, the CI still included 1. For melanoma, the all-mines SIR was 1.20. Most of the cases were in men who worked in underground mines, for whom the SIR was 0.97, but 25 occurred in men from open-cut mines, for whom the SIR was 2.02 (CI 1.31 to 2.98).

Discussion

This cohort had a lower-than-expected SIR for all cancers (0.88). Such a finding has been reported from other occupational cohorts, including one from the Australian petroleum industry, for whom the SIR for all cancers was 0.9 (CI 0.7 to 1.1).¹³ It seems likely that this finding results from an inappropriate reference population, because, as Miettinen pointed out, different selection forces were operating in the study group and the general population.¹⁴ Alternative reference groups were hard to find. Because the subjects were followed after leaving the industry a survivor bias cannot operate.

Cancer has been noted in epidemiological studies of coal miners. A study of the mortality of coal miners in the United States in the 1970s noted an increase in cancer of the stomach.¹⁵ A case-control

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study of stomach cancer in the Netherlands in 1985 failed to confirm this association.¹⁶ yet more recently, Gonzalez et al. in Spain found an odds ratio for stomach cancer in coal miners of 11.8, although the numbers were small and the CI wide (1.96 to 105).¹⁷ There was no suggestion of an increased risk of gastrointestinal cancer in the present cohort.

There have been reports of lung cancer in workers exposed to diesel fumes.^{18,19} In this cohort, the SIR for lung cancer was not elevated.

In 1988, Corbett and O'Neill reported on a cluster of cases of lymphoma in the workforce of the Huntley Colliery on the NSW South Coast.⁸ In their historical cohort study, based on NSW cancer incidence, the SIR for non-Hodgkin's lymphoma was 3.27 (CI 1.81 to 6.74) and for Hodgkin's disease 7.27 (CI 1.98 to 18.59). There was no apparent cause for this cluster of cancer and this generated considerable concern. In our statewide cohort, the SIRs for lymphoma and Hodgkin's disease were not significantly elevated. This suggests that the excess lymphoma found in the Huntley Colliery formed a cluster related to local phenomena rather than being a feature of the industry (if the occurrence was not due to chance).

Brown et al. investigated a cluster of cases of brain tumour in another NSW coal mine.⁷ In a cohort of miners from that mine the SIR for brain tumour (using Australian incidence rates) was 5.30 (CI 1.08 to 14.04) based on three cases, while the SIRs in the two neighbouring mines were 1.72 (CI 0.04 to 8.06) and 0.81 (CI 0.02 to 3.80). These mines were compared for a range of possible relevant exposures, and it was found that the index mine had ordered, and presumably used, substantially more organic solvents than the reference mines. Solvent exposure was tentatively suggested as the cause of the brain tumours, but it was recognised that the number of cases was small. The present cohort covers all mines in the state. The SIR for brain tumour was elevated for underground mines, but it did not reach statistical significance.

Hervey et al. reported that miners were overrepresented in the patients reporting to the Newcastle Melanoma Unit.¹² These authors did not appear to differentiate between underground and open-cut miners. In the current study, the data are consistent with an elevated risk of melanoma, which seems to be related entirely to open-cut mining. The obvious connection between open-cut mining and melanoma is exposure to the sun, and although the relationship is not fully understood, there is little doubt that exposure to the sun is associated with the development of melanoma. This is not unique to coal mining and illustrates again that sun-related skin disease is an occupational hazard for outdoor workers. Strategies for prevention currently exist, and in an educational program, the Joint Coal Board is actively promoting sun-protection in open-cut mines.

It appears that there is no evidence of serious hazard for cancer in modern coal mines, and in particular, no support is given to an association of mining

and haematological cancer. A risk of brain tumour still cannot be discounted, although any such risk would be small. It is likely that open-cut miners run excess risk of melanoma related to exposure to ultra-violet radiation.

Work is being done to maintain and extend the database and it is hoped that it can be analysed again in the future to provide ongoing surveillance for cancer in this important industry.

Acknowledgments

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References

1. Hunter D. *The disease of occupation*. 6th edn. London: Hodder and Stoughton, 1978.
2. Harrison JE, Frommer MS, Ruck EA, Blyth FM. Deaths as a result of work-related injury in Australia, 1982-1984. *Med J Aust* 1989; 150: 118-25.
3. Lee T, Anderson C, Kraus JF. Acute traumatic injuries in underground bituminous coal miners. *Am J Ind Med* 1983; 23: 407-15.
4. Parke WR. *Occupational lung disorders*. 3rd edn. Oxford: Butterworth-Heinemann, 1994.
5. Christie D, Brown AM, Taylor R, Soccumbi M, Conner M. Mortality in the NSW coal industry 1973-1988. *Med J Aust* 1994; 161: 19-21.
6. Corbett S, O'Neill BJ. A cluster of cases of lymphoma in an underground colliery. *Med J Aust* 1988; 149: 176-85.
7. Brown AM, Christie D, Devoy P, Nis V, Hicks MN. A cluster of brain tumours in a NSW colliery. *Aust J Public Health* 1993; 17: 200-5.
8. *Automated graphical word linkage system*. Version 3.0 [computer program]. Silver Spring, MD: Matchware Technologies, 1998.
9. Muir G, Woodward J, Mack T, Fowell J, Whiston S, editors. *Cancer incidence in five continents*. Vol. 5. Scientific publication no. 58. Lyon: International Agency for Research on Cancer, 1987.
10. SAS Version 5 [computer program]. Cary, NC: SAS Institute, 1985.
11. Miettinen JA, Gardner MJ. Calculating confidence intervals for relative risks, odds ratios, and standardized ratios and rates. In: Gardner MJ, Altman DG, editors. *Statistics with confidence: confidence intervals and statistical guidelines*. London: British Medical Journal, 1998.
12. Hervey F, Strong Z, Grant D, Marsh Z. Risk factors for presentation with thick primary melanoma include older age, male sex, smoking and may include occupation in certain industries. In: Gallagher RP, Enevad JM. *Epidemiological aspects of common malignant melanoma*. Boston: Kluwer Academic, 1994.
13. Christie D, Robinson K, Gordon J, Power A. A prospective study within the Australian petroleum industry: 2. cancer incidence. *Br J Ind Med* 1991; 48: 111-14.
14. Miettinen OS. *Translational epidemiology*. New York: Wiley Medical, 1986.
15. Rochette H. Cause-specific mortality of coal miners. *J Occup Med* 1977; 11: 793-801.
16. Swen GGH, Aarås CWFM, Baustman P, Sangen JIM, Knipsheld P. Cases of cancer in coal miners: a case control study in a coal mining area. *Br J Ind Med* 1980; 40: 687-90.
17. Gonzalez CA, Sanz M, Marco G, Pin S, et al. Occupation and gastric cancer in Spain. *Scand J Work Environ Health* 1991; 17: 340-47.
18. Gustavson P, Pato N, Lidstrom EL, Hagstvedt C. Lung cancer and exposure to diesel exhaust among bus garage workers. *Scand J Work Environ Health* 1989; 15: 143-64.
19. Scotland K, Sherman D, Beebe D. Exposure to diesel exhaust in the crushing industry and possible relationships with lung cancer. *Am J Ind Med* 1992; 21: 287-90.

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Brian Davies and Alan Rogers are independent researchers who presented at the ACGIH Sponsored International Symposium in Seattle on 6th and 7th March, research findings pertinent to their experience in the coal mining industry in New South Wales, Australia. They did not represent nor did they imply that they represented the views of the Australian Government, New South Wales Government or the NSW Joint Coal Board.

The theme of the presentation in Seattle was the last 10 years of success in implementation of monitoring and control strategies for diesel operated machinery in NSW coal mines. Information and updates were presented from 3 separate but compatible studies:

1. diesel particulate monitoring in NSW coal mines (Rogers A and Whelan W, *Elemental Carbon as a means of Measuring Diesel Particulate Matter emitted from Diesel Engines in Underground Mines, Proceedings 15th Annual Conference Australian Institute of Occupational Hygienists, 208-212, 1996*)
2. the development and successful implementation of diesel control technologies (Pratt et al including Rogers and Davies, *Evaluation and Control of Employee Exposure to Diesel Particulate at Several Australian Coal Mines, App Occup Environmental Hygiene, 12(12) 1032-1037, 1997*)
3. a lung cancer SMR of 0.7 for the NSW coal miners (Kirby W. *Joint Coal Board Cancer Study, Abstract 91, The Second International Conference on the health of Miners, Hyatt Regency Pittsburgh, November 11-13, 1995, sponsored by ACGIH, NIOSH and others.*)

During question time and also in a separate presentation to ACGIH they indicated that after more than 10 years of researching the health effects of diesel emissions, they were of the opinion that there was no definitive data on which to set a health or carcinogenic risk based exposure standard. Best practice was a viable alternative due to this lack of definitive data. Comments were offered on the often presented SMR for lung cancer of 1.4 found in some diesel studies. Comparisons were made to lung cancer SMR of 1.3 in long term high exposed asbestos workers to indicate that diesel exposures of 1.4 was much too high and therefore illogical.

They made no separate comments on the validity or otherwise of US regulatory decisions either occupational or environmental.

The comments contained in the subsequent press release appear to be selections of their comments from different aspects of the studies which have been combined and applied to the US environmental situation of which they did not specifically address at the meeting.


B. Davies


A. Rogers

cc C. Willhite, Chair ACGIH TLV Committee
W. Kirby, NSW Joint Coal Board

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**Comments on California EPA's
"Proposed Identification of Diesel
Exhaust as a Toxic Air Contaminant,
February 1998"**

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1 *Executive Summary*

OEHHA's February 1998 draft of "Part B: Health Risk Assessment for Diesel Exhaust" and the accompanying "Executive Summary" document continue to contain many components that present an unbalanced view of the scientific evidence. These are summarized below, and discussed in more detail in the sections that follow.

1.1 *The OEHHA Report Neglects the Importance of Dose*

OEHHA fails to adequately address the question of whether the levels of DE to which Californians are exposed ($1.5 \mu\text{g}/\text{m}^3$) pose a potentially toxic dose by any metric. The non-cancer health effects that are cited apply to inhaled concentrations much larger. In terms of the text of the OEHHA document that covers genotoxic effects, inadequate attention is given to the fact that considerations such as DNA repair, and baseline levels of DNA damage due to the free radical products of normal metabolism establish a practical threshold. No evidence is provided that ambient DE exposures will exceed this practical threshold.

The dose of deposited DE particulate in the lung from an exposure concentration of $1.5 \mu\text{g}/\text{m}^3$ is extremely tiny. The daily deposited dose is less than 1 particle per 100 alveoli or less than 1 particle per 600 alveolar macrophages. This level of particle deposition will be readily ingested by alveolar macrophages, with the particles isolated within phagolysosomes. Estimation of the systemic dose that this low level of DE particulate could possibly provide suggests absence of health effects. That is, the DE particulate daily dose is far less than the "no effect" levels (*e.g.*, the "reference doses") of chemicals of known toxicity such as arsenic and cyanide. No DE particulate component can be identified for which the daily dose from inhaling $1.5 \mu\text{g}/\text{m}^3$ DE particulate could be expected to exceed the reference dose for that chemical.

A comparison of the "mutagenic dose" of the diesel exhaust organics, even if completely bioavailable, shows that the quantitative dose is very small. A comparative potency analysis shows that, assuming the mutagenic activity of diesel-engine exhaust is 100% bioavailable, current diesel exhaust levels in California are equivalent to smoking one cigarette every 6 to 16 years. This would be equivalent to a person smoking **three to eight** cigarettes over a 70 year lifetime, starting at age 20. In order, for OEHHA to correctly communicate the spectrum of risks attributable to diesel-engine exhaust, it is essential that they provide such perspective in the document.

1.2 Exposure Trends are Lacking in the Meta-Analysis of DE Studies

If DE plays a causal role in the epidemiologic associations that have been reported for a variety of populations, one would expect that reported lung cancer risk across occupations would vary in proportion to estimated historical DE exposure levels. This is not the case.

The available DE measurements in occupational environments would seem to cluster occupations in three (overlapping) "order-of-magnitude" groups insofar as DE particulate concentrations ($\mu\text{g}/\text{m}^3$):

Truck drivers, dockworkers, stevedores	units-to-tens
Bus garage workers, railroad workers	tens-to-hundreds
Underground miners	hundreds-to-thousands

This ranking also makes sense in terms of the degree of access to fresh air dilution expected in these occupations. In spite of this seeming three-order-of-magnitude difference in the potential for DE particulate exposure, the reported epidemiologic relative risks for lung cancer cluster in an extremely narrow range. The discrepancy can be appreciated by a sample calculation that assumes the lung cancer risk is linear with DE concentration. For example, if DE concentrations for truck drivers in the range of $10 - 20 \mu\text{g}/\text{m}^3$ produced a relative risk 1.49 (the meta-analysis result), we can assign the 0.49 excess risk to the $10 - 20 \mu\text{g}/\text{m}^3$ exposure. Hence, DE concentrations for underground miners in the range of $1,000 - 2,000 \mu\text{g}/\text{m}^3$ should have yielded excess risks one hundred times larger or, 49, meaning that the RR for DE-exposed underground miners would be expected to be 50 (1+49), whereas reported RR's for miners in diesel-equipment mines range from 1.45 - 2.67. Such a lack of concordance argues against a causal role for DE in the reported epidemiologic associations.

1.3 Importance of Confounding by Cigarette Smoking Status

The OEHHA report fails to adequately acknowledge the diversity of scientific opinion on whether the epidemiologic associations have a causal basis. OEHHA staff may choose not to agree with scientists who conclude that the DE epidemiologic data mainly reflect residual confounding from cigarette smoke. But this is not adequate reason to merely omit presentation of these conclusions. Such omissions result in a biased presentation of the diversity of opinion on DE health effects. More analysis needs to be provided for policymakers on what the bounds of confounding due to cigarette smoking might be, and how the uncertainty in ascertainment of smoking status and in ascertainment of historical DE exposure affects the uncertainty of any dose-response estimate.

1.4 The Garshick Data Dose-Response is Likely Non-Significant

OEHHA's treatment of the Garshick data omitted important sources of variability in the "zero-exposure" risk and in the variability associated with the exposure metric. Techniques for appropriate treatment of these sources of variability are available, but were not utilized by OEHHA. A more accurate derivation that allows for these sources of variability may reveal that the value of the slope in the dose-

response curve is not statistically separable from the null value (e.g., zero slope, no trend in dose-response).

1.5 The Presentation in the OEHHA Report is not Balanced

On a number of occasions in the document, OEHHA fails to note that their interpretation of the data has important caveats, which were often stated by the original researchers.

The earlier studies of Pepelko and Peirano (1983) and of Heinrich et. al. (1986) on which OEHHA bases its conclusion that inhaled DE carcinogenicity in mice is "mixed," do not in fact warrant such a conclusion. The authors themselves and others have pointed out that the few positive results that were found in these studies cannot be assigned probative value, and that more recent studies in mice have been uniformly negative. OEHHA needs to correct its inaccurate and incomplete presentation of the mice results as being "*mixed*" by including the caveats identified by the researchers themselves.

Discussion of the bioavailability of PAHs is likewise inadequate. OEHHA's conclusion about the presence of urinary PAHs from diesel-exhaust exposure is **not** supported by the data and should not be used as evidence of bioavailability. Moreover, a simple quantitative calculation of the total quantity of PAHs that are available from DE levels at $1.5 \mu\text{g}/\text{m}^3$ shows that the daily intake of PAHs is about 1000 fold below baseline background intake of PAHs for the US population (Section 6.4). Hence a rationale for limiting PAH intake by focusing on ambient DE levels cannot be made. Moreover a rationale for limiting $\text{PM}_{2.5}$ levels in California by focusing on ambient DE levels cannot be made.

2 The OEHHA Report Neglects the Importance of “Dose”

2.1 The Report Must Refocus on Toxic Dose, not Toxic Substance

The overall presentation, both in the Executive Summary and throughout the document, goes contrary to the most fundamental principle of toxicology, namely, “the dose differentiates a poison from a remedy.” Hence, the emphasis on “toxic substance” and “toxic air contaminant” misleads readers of the report. Because any chemical is toxic at some dose, the emphasis should be on whether toxic doses of diesel exhaust will occur at ambient concentrations.

In the Executive Summary (page ES-2), the most important question to be answered about a TAC is whether toxic doses are potentially present. Yet Question #7 states: “Does the **substance** pose a potential health risk to Californians?” As stated, the question has little meaning, because all substances have the potential to pose a health risk. The more appropriate question OEHHA must address is whether the levels of DE to which Californians are exposed ($1.5 \mu\text{g}/\text{m}^3$) pose a potentially toxic dose.

2.2 “Health Effects” Summaries by OEHHA Lack Mention of “Dose” and “Threshold”

The Executive Summary lists, without caveat, a multitude of health effects (pages ES-15 to ES-22) that OEHHA attributes to diesel exhaust. Yet, virtually all of these reported effects were observed at concentrations far above what CARB is projecting as ambient exposure to diesel exhaust. The California public must not be misled in this manner. A non-expert reading the Executive Summary is left with the impression that Californians may be suffering from asthma, increased susceptibility to lung infection, glandular metaplasia, sperm anomalies, chronic respiratory disease, all caused by diesel exhaust exposures.

The Executive Summary goes on to list mutagenesis, chromosome aberrations, and DNA adducts as attributable to DE. Without giving any percentage compositions, the statement is made that “Many carcinogenic compounds are found in diesel exhaust.” OEHHA should point out that this statement can be made about any combustion product, e.g., wood smoke, charred meat. OEHHA then reaches an unsubstantiated conclusion (page ES-19) that “The genotoxic effects of diesel exhaust may be involved in the initiation of pulmonary carcinogenesis in humans.” This again is stated without any context in dose, without any consideration of baseline levels of DNA damage from normal metabolic processes, and without adequate allowance for DNA repair. An uncritical list of all such effects, regardless of the dose required to manifest them, is both erroneous and alarmist.

Throughout the Executive Summary and Part B, OEHHA equates genotoxic mechanisms of carcinogenicity with the absence of a threshold in the dose-response:

"One hypothesis invokes the genotoxicity of the compounds condensed on the surfaces of the diesel exhaust particle. This hypothesis suggests the operation of a general mechanism shared with humans and the absence of a dose-response threshold." (ES-21)

These statements do not acknowledge what is currently known about DNA repair mechanisms. Scientists (summarized by Culotta and Koshland, 1994) have identified several different types of DNA repair systems including one for DNA errors made during replication (mismatch repair), one for removing damage caused to single base pairs by substances such as oxidants (base excision repair), and one for removing large, bulky lesions such as chemical adducts (nucleotide excision repair). OEHHA notes the possibility of DNA repair following non-genotoxic damage,

"A third hypothesis is that diesel exhaust induces oxidative DNA damage by a mechanism other than particle-induced inflammation. Formation of 8-hydroxydeoxyguanosine (8-OHdG) adducts leads to G:C to T:A transversions unless repaired prior to replication" [emphasis added] (Part B, pp. 6-25)

"A fourth hypothesis is that the inflammatory response to the accumulating exhaust particles may promote cell proliferation. This would increase the probability that any existing DNA damage would result in a heritable mutation before repair could take place" [emphasis added] (Part B, pp. 6-26)

However, **no where** in OEHHA's assertion of the first hypothesis, namely:

"One hypothesis is that PAHs and nitroPAHs contained either in the semivolatile phase or adsorbed on the surface of diesel exhaust particulate matter induce lung tumors via a genotoxic mechanism." (Part B, pp. 6-25)

does OEHHA refer to the possibility of repair of these lesions. In fact, OEHHA concludes,

"Diesel exhaust-induced chronic inflammation may have a threshold of effect. However, genotoxicity induced by the PAH/nitroPAH content of diesel exhaust would not be expected to have an effect threshold." (Part B, pp. 6-29)

Because the dose to the respiratory tract of diesel particulate at ambient concentrations is so small (see our analysis below), it is unlikely that DNA repair mechanisms would be overwhelmed. Although OEHHA notes the presence or absence of a threshold for response as one of the uncertainties of the rat carcinogenicity data (ES-25), the possibility of a threshold must likewise be added to the uncertainties of human responses. The extrapolation of any data to those exposures encountered by the California population must include the probability of a threshold, regardless of the proposed mechanism of action.

2.3 Daily Lung Dose of PM is Extremely Small

CARB estimates that 1995 outdoor ambient air concentrations of diesel exhaust PM_{10} were $2.2 \mu\text{g}/\text{m}^3$, and the estimated outdoor air concentration of diesel exhaust PM_{10} for the year 2000 is $1.8 \mu\text{g}/\text{m}^3$. Using Californians' activity patterns to combine indoor and outdoor exposures, CARB estimated "total air exposure" to diesel exhaust PM_{10} to be $1.5 \mu\text{g}/\text{m}^3$ in 1995 and $1.3 \mu\text{g}/\text{m}^3$ in 2000.

First, the report should emphasize that these concentrations are less than 1/25th of the current National Ambient Air Quality Standard for annual average concentrations of PM_{10} . The PM_{10} standard was reaffirmed in 1997 by the USEPA, and fulfilled the criteria of being protective of health, even for sensitive subpopulations, with an adequate margin of safety. Second, the report and/or the Executive Summary must present some perspective on whether these concentrations can be considered to yield a "toxic dose" of diesel exhaust PM_{10} . The quantity of material deposited in the lungs from this level of air concentration is truly tiny.

What is the "dose" from this level of diesel exhaust particulate matter? The USEPA has estimated that for $50 \mu\text{g}/\text{m}^3$ of typical ambient particulate aerosol, the daily deposition in the alveolar region is about $50 \mu\text{g}$ (USEPA, 1996). Therefore, for an airborne concentration of $1.5 \mu\text{g}/\text{m}^3$, the daily dose would be about $1.5 \mu\text{g}$. The local dose of deposited particles to lung alveolar tissues can be estimated from the fact that $1.5 \mu\text{g}$ represents 2.9×10^6 unit-density, $1 \mu\text{m}$ diameter (mass median diameter) particles (each weighing 0.0005 ng).¹ This represents less than **one particle per 100 lung alveoli**. For particles of $0.2 \mu\text{m}$ mass median diameter, there would be about a one-to-one ratio of particles to lung alveoli, however, each particle would now weigh only 0.000004 ng . Because there are an estimated 2-6 lung macrophages per lung alveolus, these particles will be readily ingested by lung macrophages, sequestered in phagolysosomes, and transported out of the lungs.

Although deposition in the lungs is not completely homogeneous over the alveolar surface area of the lung (140 m^2), the $1.5 \mu\text{g}$ would yield an average dose of $0.000012 \text{ ng per mm}^2$, or 1 particle per day per 50 mm^2 lung surface for $1\text{-}\mu\text{m}$ diameter particles. The $1.5 \mu\text{g}$ of particles would cover **15 billionths** the lung surface area.² These approximate calculations illustrate that there is little opportunity for extensive particle-to-lung-cell contact, and raise the question of how "toxicity" could result from such small DE particle retention. Although these calculations assume uniform distribution of deposited particles, they do not take into account any alveolar removal processes (*i.e.*, dissolution, macrophage ingestion and transport). OEHHA has not established by what mechanism such tiny tissue doses of DE particulate could cause toxicity.

It is not expected that DE particles would be systemically absorbed. Rather, mucociliary transport and clearance by lung macrophages would deliver the particles to the throat, where they would

¹ The total mass of N unit-density particles is $(N \times \pi \times d^3/6)$. For $1 \mu\text{m}$, each particle weighs $5.24 \times 10^{-13} \text{ g}$; so 2.9×10^6 particles weigh $1.5 \mu\text{g}$. If the particles have a density **greater** than unity (which is likely the case), the numbers (and surface area) of particles in $1.5 \mu\text{g}$ of mass would be proportionately **less**.

² The projected area of each particle is given by $(\pi \times r^2)$; therefore, the area covered by each $1 \mu\text{m}$ particle is $0.78 \mu\text{m}^2$. Thus, the 2.9×10^6 $1 \mu\text{m}$ particles will cover 2 mm^2 . 2 mm^2 is **15 billionths** of 140 m^2 .

be swallowed and subsequently pass out of the body. However, even if we assume systemic absorption of the total DE particle dose, an estimate of the whole-body daily dose of DE particulate yields a very low number. As discussed above, if the total DE particulate mass deposited in the lungs in one day is 1.5 µg, and if we assume none is cleared and all is absorbed, then the daily systemic dose would be 0.000 02 mg/kg (for a 70-kg person). Moreover, the dose of individual organic species on DE particles would be a small fraction of this total particulate mass. What chemical constituent of DE can cause toxicity at this daily dose level? The daily dose of pure arsenic judged to be without adverse health effects is fourteen-fold larger than this (As, RfD = 0.0003 mg/kg). The daily dose of cyanide judged to be without adverse health effects is 1,000 times larger than this (HCN, RfD = 0.02 mg/kg). OEHHA needs to provide comparisons of this kind so that policymakers and the public will be able to place claims made in the document about DE toxicity in perspective.

2.4 Comparative Potency of Organics is Extremely Small

Another way to evaluate DE dose is to estimate the "mutagenic dose" of DE-particle-associated organics to the respiratory tract. That is, even if **all** the adsorbed organic substances were freely bioavailable (which they are not), what is the quantitative dose in terms of "mutagenic risk" in perspective to known sources of "mutagenic risk?"

Analysis #1

To place the issue of relative risk into context, one can take mutagenicity data obtained by the U.S. Environmental Protection Agency (EPA) on cigarette smoke and diesel engine exhaust (Lewtas *et al.*, 1981; Austin *et al.*, 1985), compare their specific mutagenic activities, and estimate the mutagenic dose to the lungs. Cigarette smoke condensate (CSC) was derived from Kentucky Reference, Type 2R1, research cigarettes. These cigarettes were 85 mm in length, non-filtered, with a tar content of 36.6 mg/cigarette, and representative of those cigarettes smoked from 1962 - 1966. Diesel-engine exhaust extract (DEEE) was derived from a light-duty diesel passenger vehicle (Oldsmobile 350, model year unspecified) using No. 2 diesel fuel. The vehicle was not equipped with a catalytic converter or exhaust gas recirculator. An average of 14.5% of the particle mass was extractable using Soxhlet extraction procedures. The mutagenicity of CSC and DEEE was tested using the TA98 strain of *Salmonella typhimurium*. The condensate and extract were tested with and without the addition of S-9.

Table 2-1: Comparison of Mutagenic Activity of Cigarette Smoke Condensate and Diesel-Engine Exhaust Extract (from Austin *et al.*, 1985)

Substance	Percent Extractable	Revertants/Microgram	
		Without S-9	With S-9
Cigarette Smoke Condensate	100	0	1.1
Diesel-Engine Exhaust Extract	14.5	2.1	1.4

Table 2-1 shows the specific mutagenicity on a per mass basis of CSC and DEEE (Austin *et al.*, 1985). These data show that on a per microgram basis, the specific activity of DEEE was higher than CSC. The mutagenic activity of CSC required the S9 enzyme fraction, whereas DEEE did not require the S9 enzyme fraction.

To place the mutagenic risk of cigarette smoke and diesel-engine exhaust in perspective, one needs to compare the relative "doses" of mutagenic activity upon inhaling cigarette smoke or diesel-engine exhaust. We calculated mutagenic "dose" using the amount of mutagenic activity, expressed in "revertants" deposited in the lungs.

Mutagenic dose from cigarette smoke. Lewtas *et al.* (1981) estimated that approximately each cigarette yielded 20 mg of condensate. If the specific activity of the condensate was 1.1 revertants/ μg (Table 2.1), then one cigarette contains 22,000 revertants. In the human respiratory tract, the deposition efficiency of inhaled cigarette smoke is approximately 50% (Hinds *et al.*, 1983). Thus, the "mutagenic dose" of one cigarette is 11,000 revertants.

Mutagenic dose from inhaled diesel-engine exhaust. Diesel-engine exhaust extract had a specific mutagenic activity of 2.1 revertants/ μg ; thus, it would take 5,238 μg of deposited DEEE to be equivalent to the deposited mutagenic activity from one cigarette (that is, 11,000 revertants). Because diesel exhaust particles contained only 14.5% extract, it would take 36,125 μg of exhaust particles to obtain 5,238 μg of extract. The deposition efficiency of inhaled DEE is approximately 20% (Yu and Xu, 1987). Thus, an individual would have to inhale 180,625 μg (181 mg) of DEE to achieve an equivalent mutagenic dose as one cigarette.

Using the data set from Table 2.1, we can determine how many years it would take for an individual to inhale diesel exhaust at current ambient concentrations to equal smoking one cigarette. The CARB estimated that the 1995 average total air exposure concentration is 1.5 $\mu\text{g}/\text{m}^3$ (Executive Summary, pp. 13). At 1.5 $\mu\text{g}/\text{m}^3$, a person would have to breathe 120,416 m^3 of air to inhale 181 mg of particulate. Assuming a breathing rate of 20 m^3/day (average for adults breathing at rest, during light exercise, and during sleep), it would take an individual 6,021 days or **16 years and 5 months** to inhale an equivalent mutagenic dose as found in one cigarette.

The advantage of using data from the study by Lewtas *et al.* (1981) and Austin *et al.* (1985) is that the mutagenic assays were conducted in the same laboratory, thus eliminating study to study variations. However, the cigarettes and diesel exhaust used in this investigation were representative of the substances people were exposed to in the 1960's. Currently, people are exposed to substances with different properties (for example, low-tar cigarettes, low-sulfur fuels). We can repeat this analysis using substances representative of the 1990's. The disadvantage is that smoking and diesel exhaust data will be taken from different laboratories, which is not as ideal as the U.S. EPA investigation. In addition, the lung cancer risk of cigarettes manufactured in the 1990's and currently being smoked is not known. We, therefore, repeated our analyses a third time using the older 2R1 cigarette, which is representative of a proven lung cancer hazard, and contemporary diesel fuel.

Analysis #2

Data for CSC mutagenicity was taken from Steele *et al.* (1995). These investigators evaluated the mutagenicity of the Kentucky Reference cigarette 1R4F. These cigarettes are 84 mm in length, filtered, and representative of filtered cigarettes currently smoked. Data for DEEE mutagenicity was taken from Bagely *et al.* (1996). Bagely and coworkers assessed the mutagenicity of a "conventional" fuel (sulfur = 0.32% by weight; aromatics = 22% by volume; cetane number = 53) and a "low-sulfur" fuel (sulfur = 0.01% by weight; aromatics = 30% by volume; cetane number = 42) in a 1988 Cummins L10 engine. Both fuels were more similar to the "alternative formulation" than to the "pre-1993" or "low aromatic" fuels tested by CERT. The TA98 tester strain was used by both sets of investigators to assess mutagenicity of the CSC and DEEE.

Table 2.2: Comparison of Mutagenic Activity of Cigarette Smoke Condensate and Diesel-Engine Exhaust Extract Using Contemporary Substances (Steele *et al.*, 1995; Bagely *et al.*, 1996)

Substance	Percent Extractable	Revertants/Microgram	
		Without S-9	With S-9
Cigarette Smoke Condensate ^a	100	NA ^b	1.5
Diesel-Engine Exhaust Extract (conventional fuel) ^c	27	2.2	NA ^b
Diesel-Engine Exhaust Extract (low-sulfur fuel) ^c	29	1.9	2.0

^a Data from Steele *et al.*, 1995. Average of nonlinear and linear regression models.

^b Data not available.

^c Data from Bagley *et al.* 1996. Engine load = 75% (EPA rated mode 9).

Mutagenic dose from cigarette smoke. Steele *et al.*, (1995) also reported the mutagenic activity on a per cigarette basis. The authors estimated that the smoke from one cigarette contained 15,000 revertants (average of nonlinear and linear regression models). Again, assuming that the deposition efficiency of inhaled cigarette smoke is approximately 50%, then the mutagenic dose of one K1R4F cigarette is 7,500 revertants.

Mutagenic dose from inhaled diesel-engine exhaust. Diesel-engine exhaust extract from the conventional fuel had a specific mutagenic activity of 2.2 revertants/ μg ; thus, it would take 3,409 μg of deposited DEEE to be equivalent to the deposited mutagenic activity from one K1R4F cigarette (that is, 7,500 revertants). Because the diesel particulate contained only 27% of extract, it would take 12,626 μg of exhaust particles to obtain 3,409 μg of extract. Again, using a deposition efficiency of 20% for inhaled DEE, an individual would have to inhale 63,130 μg (63 mg) of DEE to achieve an equivalent mutagenic dose of one K1R4F cigarette.

Diesel-engine exhaust extract from the low-sulfur fuel had a specific mutagenic activity of 1.9 revertants/ μg ; thus, it would take 3,947 μg of deposited DEEE to be equivalent to the deposited mutagenic activity from one K1R4F cigarette (that is, 7,500 revertants). Because the diesel particulate contained only 29% of extract, it would take 13,610 μg of exhaust particles to obtain 3,947 μg of extract. Thus, an individual would have to inhale 68,052 μg (68 mg) of DEE to achieve an equivalent mutagenic dose of one K1R4F cigarette.

Using the data set from Table 2.2, we can determine how many years it would take for an individual to inhale diesel exhaust at current ambient concentrations to equal smoking one K1R4F cigarette. Again, using CARB's estimate of $1.5 \mu\text{g}/\text{m}^3$ (1995 average total air exposure concentration), a person would have to breathe $42,087 \text{ m}^3$ of air containing diesel particulate derived from conventional fuel and $45,368 \text{ m}^3$ of air containing diesel particulate derived from low-sulfur fuel to obtain the respective amount of particulate. Translating these values to time (using $20 \text{ m}^3/\text{day}$), we calculate that it would take an individual 2,104 days or **5 years and 9 months** (conventional fuel) or 2,268 days or **6 years and 2 months** (low-sulfur fuel) to inhale an equivalent mutagenic dose as found in one K1R4F cigarette.

Analysis #3

As discussed above, we also calculated the relative mutagenic risk using the older 2R1 brand of cigarette and a fuel with contemporary characteristics. We selected mutagenicity data from Bagely's low-sulfur fuel.

Mutagenic dose from cigarette smoke. We calculated that the mutagenic dose of one 2R1 cigarette was 11,000 revertants.

Mutagenic dose from inhaled diesel-engine exhaust. Diesel-engine exhaust extract from the low-sulfur fuel had a specific mutagenic activity of $1.9 \text{ revertants}/\mu\text{g}$; thus, it would take $5,789 \mu\text{g}$ of deposited DEEE to be equivalent to the deposited mutagenic activity from one cigarette (that is, 11,000 revertants). Because the DEE contained only 29% of extract, it would take $19,964 \mu\text{g}$ of exhaust particles to obtain $5,789 \mu\text{g}$ of extract. Using a deposition efficiency of 20% for inhaled DEE, an individual would have to inhale $99,819 \mu\text{g}$ (100 mg) of DEE to achieve an equivalent mutagenic dose of one cigarette.

We can determine how many years it would take for an individual to inhale diesel exhaust at current ambient concentrations to equal smoking one 2R1 cigarette. Using CARB's estimate of $1.5 \mu\text{g}/\text{m}^3$ (1995 average total air exposure concentration), a person would have to breathe $66,546 \text{ m}^3$ of air containing diesel particulate derived from low-sulfur fuel; it would take an individual 3,327 days or **9 years and 1 months** to inhale an equivalent mutagenic dose as found in one 2R1 cigarette.

Conclusion

We conducted a series of three analyses showing the relative mutagenic risk between diesel-engine exhaust and cigarette smoke. Our analyses assumed that **all** the organic material extractable from DE particles is bioavailable. Because of the low bioavailability (discussed in our Section 6.3), this is a dramatic overestimate of the fraction of DE particle organics removable by physiological fluids. The type of cigarette brand and diesel fuel (as well as other factors, such as puff volume, engine type, etc.) affects the relationship between the amount of diesel-engine exhaust one needs to inhale at current ambient levels before it is equivalent to smoking one cigarette. The analyses shows that, even assuming the mutagenic activity of diesel-engine exhaust is 100% bioavailable, current diesel exhaust levels in California are equivalent to smoking one cigarette every **6 to 16 years**. This would be equivalent to a person smoking **three to eight** cigarettes over a 70 year lifetime, starting at age 20. In order, for OEHHA

to correctly communicate the spectrum of risks attributable to diesel-engine exhaust, it is essential that they provide this perspective in the document.

3 Exposure Trends are Lacking in the Meta-Analysis of DE Studies

3.1 Occupational DE Exposure Estimates are Weak or Missing

Our ability to find any dose-response for DE in the epidemiologic studies is seriously undermined by the fact that actual DE exposure levels are not available for any of the study populations. Moreover, the RRs reported for lung cancer for a variety of occupations are unexpectedly similar, even though the range of DE exposures from occupation to occupation must have been large. To illustrate this problem, we developed Table 3.1, described in the following sections, and such a table should be included in OEHHA's presentation of the DE epidemiology data.

When we evaluate lung cancer risks reported in potentially DE-exposed populations, it is essential to recognize three characteristics of the DE epidemiology:

- **None** of the epidemiology studies include measurements of diesel exhaust concentrations for the study populations. On our Table 3.1, the separation of the lung cancer risk columns and the columns for DE concentration emphasizes the absence of direct correlation along the rows for specific occupations. For the epidemiologic studies, the potential for DE exposure was indirectly assessed from union records, interviews, questionnaires, and death certificates.
- Most of the epidemiologic studies have inadequate (or nonexistent) control for confounders such as personal smoking habits, ETS exposure, or ambient/occupational airborne particles.
- As discussed elsewhere in this document, the epidemiologic studies do not allow for statistical error either in the (surrogate) DE exposure categories or in the RR of the control group, and thus underestimate the total statistical error in the reported RR estimates.
- On the (separate) studies attempting to quantify DE exposure, most of the measurements relate to **"particulate concentrations."** Investigators have attempted in various ways to correct for other sources of ambient particulate such as dust or ETS, but it should be remembered that the entire reported concentration may not be DE particulate.

3.2 DE Exposures and Reported Lung Cancer Risks by Occupation

The epidemiologic literature on occupational exposure to DE is extensive, and we primarily utilized the reviews by Cohen and Higgins (1995), Muscat and Wynder (1995), Abel and Stober (1996), The World Health Organization (WHO, 1996), and Bhatia *et al.* (1998) to collect the information presented below. The individual studies we identified within these sources are given in the reference list. To limit the number of studies used, we selected only studies published after 1980. Because numerous studies of relative risk and of diesel concentrations are available for several occupational groups, we selected the more recent studies in an attempt to get a closer match between the epidemiologic study population and the available DE exposure measurements for the studied occupation. It is important to stress, however, that the majority of the DE particle concentration data were obtained many years later than when the actual DE exposures occurred for the epidemiologic population. The mismatch between worker historical DE exposures and much later measurements of air particulate concentrations limits the conclusions that can be drawn by comparing lung cancer risks reported for various occupations with reported levels of particulate exposure.

Often, within each epidemiologic study, several estimates of lung cancer risk are reported. Some of the different risk estimates were based on different worker subpopulations or on estimated differences in potential for DE exposure. When multiple risk values were given in the secondary sources we consulted, we attempted to record in Table 3.1 the range of risk estimates that encompassed the largest segment of the DE-exposed study population. For certain occupations, the meta-analysis results from Bhatia *et al.* (1998) were available.

3.3 Lack of Concordance between RR's and Likely DE Exposures

Table 3.1, on the next page, lists seven separate occupations where workers are potentially exposed to DE. The first column lists the description of the occupation plus the meta-analysis result for RR from the recent study by Bhatia *et al.* (1998). The next three columns list RRs from some of the individual studies. The last three columns list DE particle concentrations that have been measured for each of the occupations, albeit in studies that were generally separate in location and time from the epidemiologic studies. The important result shown by this table is that there is a lack of concordance between the level of reported lung cancer risk and the best estimated of DE particle concentrations in the various occupations.

Tbl. 3.1. Comparison of Reported Lung Cancer RR's for Various Occupations with the Reported Diesel Exhaust Concentrations for Those Occupations

Occupation (RR = meta analysis from Bhatia et al, 1998)	Reported Lung Cancer Risk (RR, SMR, OR)	Dates of Study Period	Reference (1 st author, date)	Particle Concentration (µg/m ³)	Dates of Particle Meas.	Reference (1 st author, date)
Bus Garage Workers (RR = 1.24)	0.90	1950 - 1974	Waller, 1981	14 - 326 ^a	~1989	USNIOH, 1990
	1.01	1967 - 1975	Rushon, 1983	300 - 1,200	~1984	Waller, 1985
Dockworkers / Stevedores	0.97 - 1.27	1945 - 1970	Gustavsson, 1990	220 - 370 ^a	~1989	Blome, 1990
	1.34 - 2.43	1945 - 1970	Gustavsson, 1990	10 - 370 ^a		Gamble, 1987
Heavy Equipment Operators (RR = 1.11)	1.32	1961 - 1980	Gustafsson, 1986	13.8 ^b	1989	Zaebst, 1991
	2.7 - 6.8	1960 - 1982	Emmelin, 1993	1.9 - 24 ^b	1990	Zaebst, 1990
Railroad Workers (RR = 1.44)	0.94 - 1.64	1982 - 1984	Wong, 1985	(no occupation-specific exposure data are available)		
	2.60	1982 - 1984	Boffetta, 1988			
Truck Drivers (RR = 1.49)	2.1	1982 - 1987	Hayes, 1989			
	1.20 - 1.35	1965 - 1977	Howe, 1983	95% Confidence Int. ^c	~1983	Woskie, 1988
Underground Miners	1.11 - 1.41	1981 - 1982	Garshick, 1987	dispatchers: 31-35		
	1.20 - 1.72	1959 - 1980	Garshick, 1988	signalers: 50-66		
Railroad Workers (excluding shopworkers)	1.59	1982 - 1984	Boffetta, 1988	engineers: 65-77		
	1.34 - 1.82	1959 - 1980	Garshick, 1988	brakers/cond.'s: 83-95	~1983	Woskie, 1988
Truck Drivers (RR = 1.49)	1.53	1954 - 1970	Walrath, 1985	(see above)		
	1.24	1982 - 1984	Boffetta, 1988		1989	Zaebst, 1991
Underground Miners	1.5	1982 - 1987	Hayes, 1989	3.8 ^b		USNIOH, 1989
	0.94 - 1.83	1982 - 1983	Steenland, 1990	33 - 94 ^a		
Underground Miners	1.60	1970 - 1980	Hansen, 1993			
	2.1 - 2.5	1970 - 1980	Swanson, 1993			
Underground Miners	2.1	1980 - 1982	Lerchen, 1987	900 - 1,900 ^d	~1989	Bagley, 1990
	2.67	1982 - 1984	Boffetta, 1988	660 - 940	~1988	Watts, 1989
Underground Miners	1.45	1982 - 1984	Ahlman, 1991	550 - 1,920	~1989	Rubow, 1990
				830 - 1,740	~1992	Amb, 1994

Notes: ^a Respirable elemental carbon; ^b Geometric mean elemental carbon; ^c Respirable particulate corrected for cigarette smoke but not for non-diesel particles; ^d In the case of measurements from mines, smoking was not allowed underground, and using the "submicrometer" particle size range excluded mine dust.

3.4 Implications for Conclusions about Causality

The data available on DE particle concentrations in occupational settings were obtained at a later date than when the actual DE exposures occurred for the worker populations in the epidemiologic studies. Investigators have not attempted to extrapolate available measurements back to historical DE exposures, with the sole exception of the railroad workers, where OEHHA has developed some estimates of historical DE exposure levels.

However, it is remarkable that the range of relative lung cancer risks associated with DE occupations by the various studies cover such a small range. That is, the reported results cluster in the range from no added risk (1.0), up to about a doubling of risk (2.0), with a few values above this level. In fact, the summary meta analysis value for all DE epidemiologic studies is 1.33, with a range of 1.11 to 1.49 in the subanalysis by occupation (Bhatia *et al.*, 1998). It is biologically implausible that, if DE were (causally) increasing lung cancer risk by 50% for low exposure (say, truck drivers), then the lung cancer risk DE produced in a more heavily exposed worker populations (railroad workers, miners) would be found to fall in this same range of added risk.

The available particle concentration measurements would seem to cluster the occupations in three (overlapping) "order-of-magnitude" groups insofar as DE particulate concentrations ($\mu\text{g}/\text{m}^3$):

Truck drivers, dockworkers, stevedores	units-to-tens
Bus garage workers, railroad workers	tens-to-hundreds
Underground miners	hundreds-to-thousands

This ranking also makes sense in terms of the degree of access to fresh air dilution expected in these occupations. In spite of this seeming three-order-of-magnitude difference in the potential for DE particulate exposure, the epidemiologic relative risks cluster in an extremely narrow range. The discrepancy can be appreciated by a sample calculation that assumes the lung cancer risk is linear with DE concentration. For example, if DE concentrations for truck drivers in the range of 10–20 $\mu\text{g}/\text{m}^3$ produced a relative risk 1.49 (the meta-analysis result), we can assign the 0.49 excess risk to the 10 – 20 $\mu\text{g}/\text{m}^3$ exposure. Hence, DE concentrations for underground miners in the range of 1,000 – 2,000 $\mu\text{g}/\text{m}^3$ should have yielded excess risks one hundred times larger or, 49, meaning that the RR for DE-exposed underground miners would be expected to be 50 (1+49), whereas reported RR's range from 1.45 – 2.67. Such a lack of concordance argues against a causal role for DE in the reported epidemiologic associations.

The reasons for doubting causality with regard to the epidemiologic results for DE-related occupations are well known. They have to do with flawed methodology (lack of adequate control for smoking), values for RR that are low and often not statistically elevated above 1.0, inadequate treatment of sources of variability, and poor control over how authors chose to define DE exposure surrogates (that is, job category within a profession, cumulative years of work, age at time of exposure, *etc.*).

Although it is instructive to compare reported lung cancer risks with occupational DE concentrations, we are left, unfortunately, with the reality that we do not have quantitative measures of DE exposure for the study populations at the time they were exposed. Changes in factors such as diesel fuel formulation, engine design, workplace ventilation, and worker smoking habits hinder retrospective application of the values for chronologically later measurements of DE particulate levels. Although the data suggest that DE concentrations by occupation span a far greater spectrum of values than do occupation-specific risk estimates, the meaning of this lack of concordance must be assessed with caution.

4 Importance of Confounding by Cigarette Smoking Status

4.1 Weakness of Low Relative Risks

OEHHA does not make clear in the document that the epidemiologic studies could plausibly be showing an artifactual association between the lung cancer risks and diesel exhaust. Moreover, as discussed subsequently in the context of our Fig. 1, lung cancer RRs for occupational "control groups" can vary over a range from 0.4 to 2.7, presumably due to differences in smoking and other lifestyle factors. Therefore, the level of RRs being reported in the DE epidemiology fall within this level of natural variation.

4.2 Literature Analyses of the Importance of Smoking Assessment

It is surprising that after this many drafts of the document, OEHHA still fails to provide citations to and discussion of articles that emphasize the importance of possible confounding by cigarette smoking. In order to provide the California public and policymakers a full perspective on the issue, it is important for OEHHA to acknowledge the validity of dissenting opinions about the DE epidemiology.

Currently, OEHHA dismisses the analyses of other reviewers with the comment "OEHHA staff disagree with the conclusions reached by these authors" (Page C-OEHHA-92). At the very least, the conclusions of such authors should be given in the document, and a brief statement from OEHHA should be given as to why the analyses whose conclusions differ from those of OEHHA must be flawed. Otherwise, the document will present an unbalanced view of the scientific thinking on the subject of whether DE poses a lung cancer risk for Californians or not. Their presentation should include the following excerpts:

- *"Because of the overwhelming effect of cigarette smoking, population-based studies that report on environmental effects, particularly at relatively low levels of excess risk (RR greater than 1.0 but less than 2.0), and that do not attempt to take cigarette smoking into account, must be considered seriously flawed." (Speizer, 1986).*
- *"Despite the evidence for carcinogenicity of diesel exhaust in human populations, assessment of lifetime exposure to diesel has been limited by the absence of a specific marker for diesel exhaust, and scanty data on historical exposures. these deficiencies have weakened the ability to develop quantitative risk estimates from the epidemiologic data." (Schenker, 1989)*

- *“Because cigarette smoking is the predominant cause of lung cancer, studies of diesel exhaust and lung cancer require precise statistical adjustment for cigarette smoking. ... Zang and Wynder calculated that men who smoked > 20 pack-years have an odds ratio of lung cancer that varies from 26.9 to 48.4 depending on their lifetime intake. ... Apparently the low relatively elevated odds ratios in studies of diesel engine exhaust and lung cancer may be confounded by incomplete statistical adjustment for smoking.” (Muscat and Wynder, 1995).*
- *“Today, it is commonly recognized that in epidemiological studies of lung cancer risk for causes other than smoking, the control of smoking as a confounding factor is of overwhelming importance, especially when dealing with occupational risks. ... It is therefore somewhat astonishing that the majority of [the diesel exhaust] cohort studies [listed in Table 2 of Stober and Abel] did not take smoking habit into account. These studies do not contribute unbiased evidence to the diesel exhaust epidemiology. ... In the studies performed, vehicle exhausts do not exhibit any clear, statistically significant, and consistent effect on the lung cancer risk of people who have a high level of exposure to these exhausts.” (Stober and Abel, 1996)*
- *“A key contribution is to show how recent techniques developed in the artificial intelligence and statistics literature can help clarify the causal interpretation of complex multivariate data sets used in epidemiological risk assessments. Applied to the key study of Garshick et al. (1988), these methods show that DE concentration has no positive causal association with lung cancer mortality risk.” (Cox, 1997)*
- *“Although there have been a number of papers suggesting that diesel fumes may act as a carcinogen, the weight of the evidence is against this hypothesis. ... In spite of the vast number of published epidemiological studies, none has provided convincing evidence that there is an increased risk of cancer from diesel exhaust emissions. ... It is abundantly evident that there is no consistency in the various mortality studies that have been reviewed; moreover, the strength of the various associations found was low. The modest excesses in relative risk around 1.3 -- 1.8, a range in which it is virtually impossible to assign a cause and effect relationship because of confounding factors. There have been no recent publications that permit more definite conclusions.” (Morgan, et al. 1997)*

In order to provide policymakers and the public with a balanced view of the issue, it is essential that OEHHA quote the conclusions of authors who have come to markedly different conclusions after reviewing the same epidemiologic data.

4.3 *Ease with which Low Relative Risks Arise*

Low relative risks can readily arise from incomplete adjustment for strong confounders. P.N. Lee has studied this problem quantitatively, and concluded:

"In any non-randomized epidemiological study with a relative risk less than 2, great care must be taken before inferring causality. The closer the relative risk is to 1, the more severe the problems of interpretation due to one or more of the various sources of bias. ... Until more attention is paid to these points, it will remain likely that many reports of statistically significant but weak associations will be false-positives." (Lee, 1989)

Also, as Lee points out: ***"Only if a confounder is measured without error, can it be assumed that it cannot explain the association."*** (Ibid., p.53)

Lee also developed a formula by which the effect of confounding can clearly be seen. For example, if 70% of the "exposed" group are smokers, and only 40% of the "control" group are smokers, and if the RR of smoking is 20, then an apparent RR of 1.66 will arise from the smoking discrepancy, without any effect of the exposure itself. Smaller differences in the prevalence of smoking in the two groups will give rise to smaller artifactual RR's, but the effect from confounding by lack of adequate control of smoking is significant. Even if statistical adjustment for smoking is made, it may not eliminate the effect of the confounder, because there is no way to assure that the confounder has been "measured without error."

5 The Garshick Data Dose-Response is Likely Non-Significant

5.1 The Referent Population is Not the Same as the Diesel Exhaust Exposed Population

As shown in the attached Figure 5.1, which summarizes occupational studies identified by Park *et al.* (1991), the relative risk of lung cancer in the **control** groups can vary over a range from about 0.4 to 2.8. That is, among "no exposure" groups selected within occupations, the "noise" level for lung cancer relative risks among groups is large. Park and co-authors concluded that:

"In 109 industrial cohorts largely free of work-related mortality, [these] selection effects were sizeable for both malignant and nonmalignant outcomes."

Consequently, to say that the inter-comparison of the separate groups of workers within the Garshick study for dose response purposes (as done by OEHHA), results in a statistically significant dose response is highly questionable. What looks like an "exposure-response" could be due entirely to a time trend in the **control** group. Moreover, the overall lung cancer RRs reported in the Garshick study do not fall outside the "noise range" of RRs among for non-exposed worker groups.

5.2 No Uncertainty was Included for Two Important Parameters of the Dose-Response Fitting

OEHHA's fitting of the Garshick data has overlooked completely two major sources of variability.

As can be seen from Figures F-2 to F-4 in the OEHHA document, both the y-intercept (relative risk at zero years of DE exposure), and x-values of the exposure metric (Years of DE Exposure) are plotted with zero variability. As discussed above, the paper by Park *et al.* (1991) showed clearly that the relative lung cancer risk of the control and exposed cohorts cannot be assumed to be identical with 1.0 at zero exposure. What Park *et al.* showed was that the relative risk for lung cancer mortality among 79 "unexposed" cohorts varied by nearly a factor of five. The very fact that the two cohorts in the Garshick study are two different groups of people, with different jobs, life histories, etc., means that it is impossible that they have no differences in baseline lung cancer risk under the "unexposed" scenario.

Furthermore, the ascertainment of years of exposure has uncertainty and variability associated with it, and it is erroneous to fit this parameter as if it were perfectly known. Because OEHHA has not included the variability in these parameters, OEHHA's fitting will not yield a statistically valid result.

OEHHA's approach has the effect of artefactually increasing the statistical significance of the slope of the dose-response curve. Appropriate statistical methods to derive dose-response curves are available (Lash et. al., 1996), but were not used by OEHHA. A more accurate derivation that allows for these sources of variability may reveal that the value of the slope in the dose-response curve is not statistically separable from the null value (e.g., zero slope, no trend in dose-response).

5.3 The "Saturation" Exhibited by the OEHHA Dose-Response Curve Supports Non-Causal Basis for the Association

In order to biologically justify the strange appearance of the dose-response curves (OEHHA Figures F-2 to F-4), OEHHA claimed at a recent public meeting with the SRP that, "cigarette smoking relative risk also shows a saturation after about 150 pack years of smoking." This is just not the case. Our Figure 5.2, which is a copy of Figure 11 in Thun et al. (1997) shows that for both men and women, the mortality rate for lung cancer increases both with smoking intensity and duration of smoking, with no hint of saturation. Therefore, the derived appearance of OEHHA's diesel exhaust dose-response curve is biologically implausible and is not supported by this example.

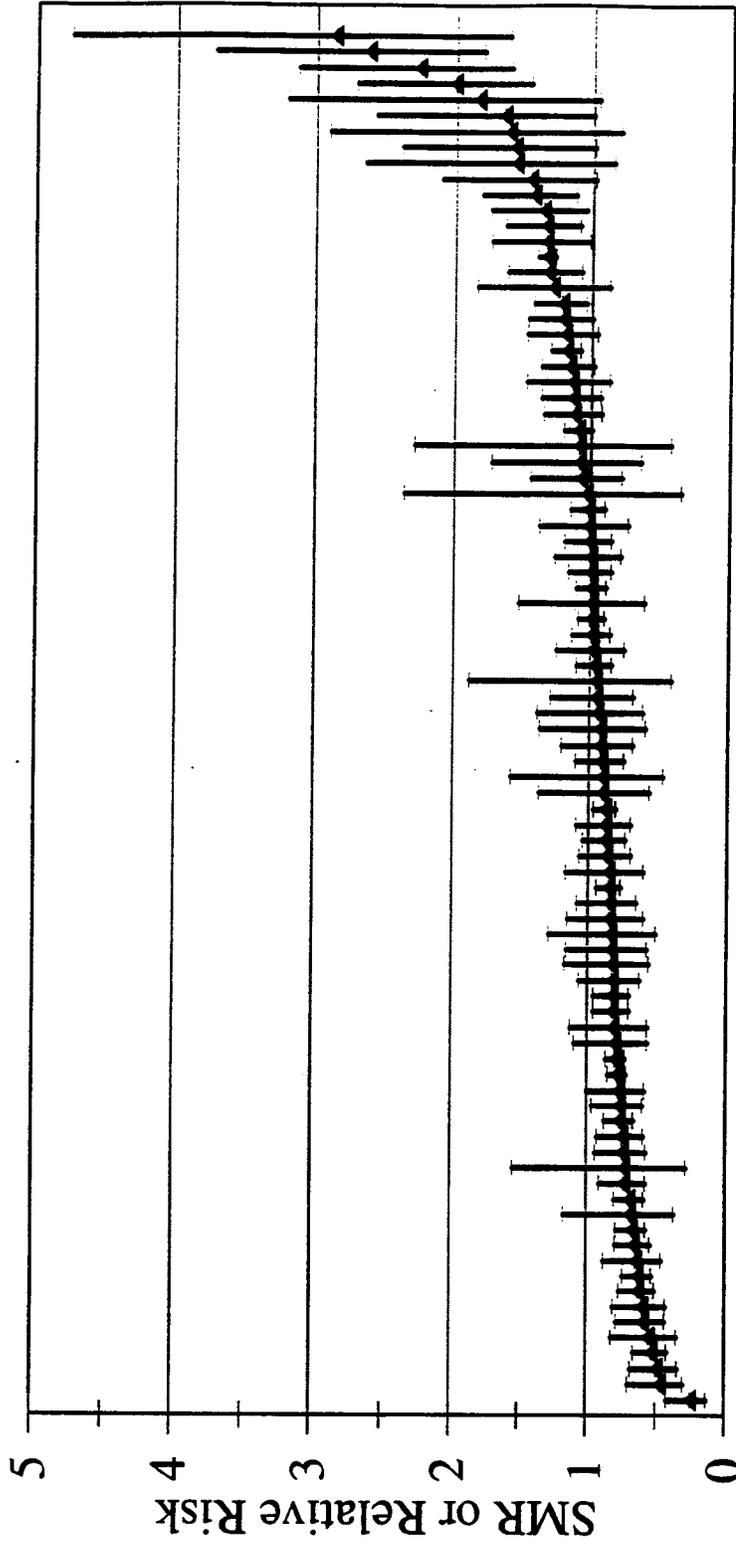
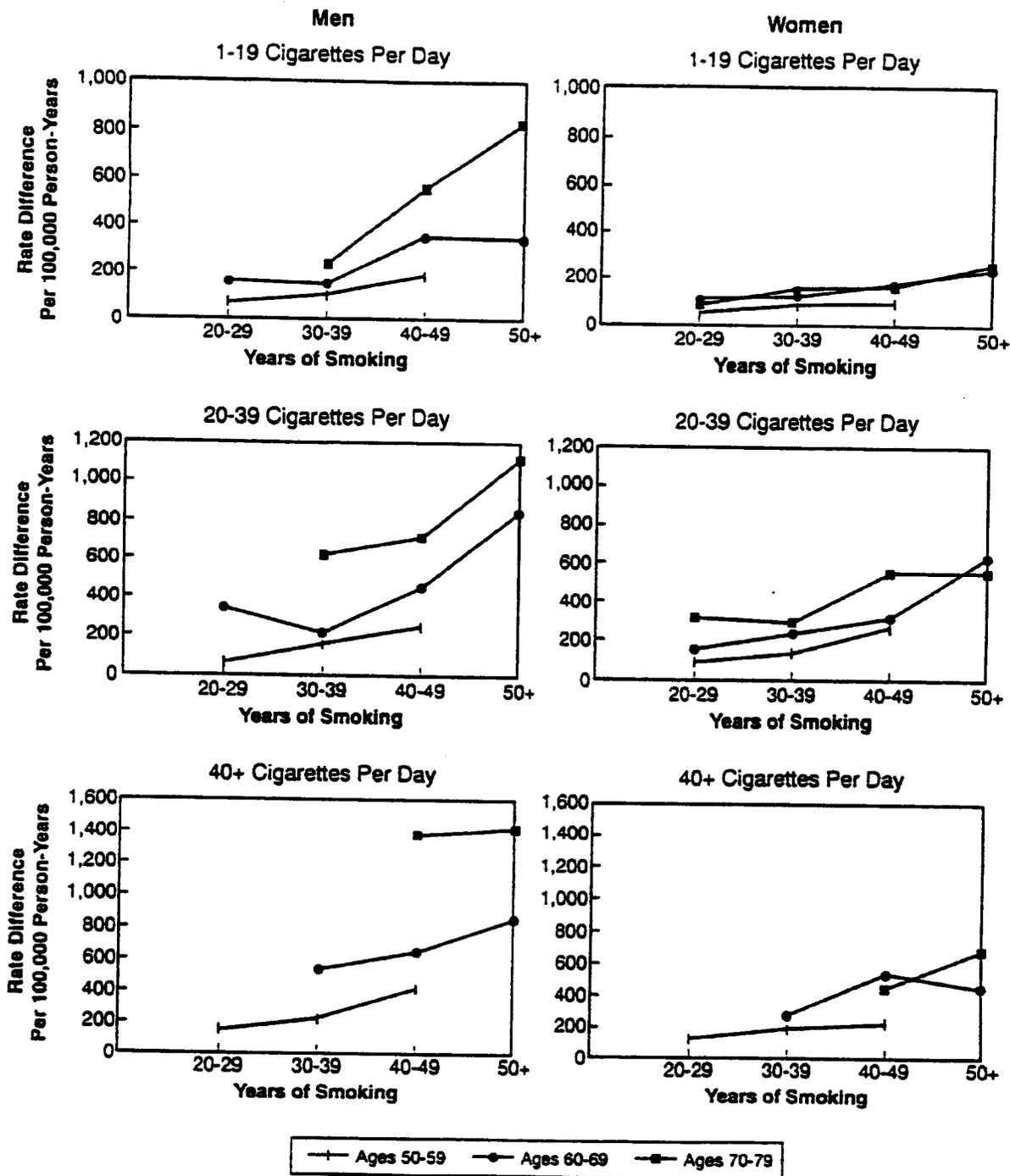


Figure 5.1 Vertical Axis: Relative Risks (Maximum Likelihood Estimate, 90% CIs) for Lung Cancer in 88 Occupational Control ("No-Exposure") Groups. Horizontal Axis: Sequential ordering of MLE estimates from lowest to highest (From studies identified by Park *et al.* 1991)

Figure 5.2 Dose-response for lung cancer caused by cigarette smoke. Excerpted from Thun *et al.* (1997).

excess death rates (RD) from lung cancer, by age, years of smoking, and cigarettes per day—
Cancer Prevention Study II: Duration fixed at time of enrollment^a



^a Graphs portray only positive RD values based on cells containing three or more deaths in smokers and never-smokers.

6 *The Presentation in the OEHHA Report is Not Balanced*

6.1 *Low RR's Support Association, Not Causality*

OEHHA has attempted to bolster the significance of the weak associations reported for diesel exhaust by comparing them to the associations of smoking with cardiovascular disease, for which OEHHA tabulates RR's covering the range 1.3 to 2.08 (Page C-OEHHA-19, and Part B, 6-53). This example is not an accurate one.

A recent review of the smoking data (Thun et al, 1997) showed that reported RRs for coronary heart disease in smokers range up to 6.3 in men and 7.2 in women, with the British Doctors Study (Doll and Hill, 1966), and the CPS-I study (Hammond, 1966) reporting more than 30 years ago that the death rates from coronary heart disease were 5.7 times higher among cigarette smokers than nonsmokers for the ages 35-44. Thus OEHHA's claim that this recognized connection is based only on "weak" and "very weak" epidemiological data is wrong.

Furthermore, many counterexamples could be given, *i.e.*, situations where weak RRs point to associations that are non-causal. One contemporary example is the association that epidemiologic studies have reported between childhood cancers and power-line electric and magnetic fields (EMFs), an issue that has caused much unwarranted public alarm and anxiety. Epidemiologic studies have reported EMF relative risks for childhood leukemia, in multiple populations, that have ranged from 2.4 (N. Wertheimer) to 1.5 (D.Savitz) to 2.2 (S. London) to 3.8 (M. Feychting). Yet, in a recent National Academy of Sciences review (NAS, 1996), the expert review group concluded that even though the weak associations are repeatedly seen, it is highly unlikely that there is any causal link with power line electric and magnetic fields. Furthermore, a recent NCI study by Linet and colleagues reported non-significant RRs of 0.9 and 1.2 for childhood leukemia and EMF (Linet *et al.*, 1997). Thus, the mere pattern of a series of weak epidemiological results cannot, of itself, support causality.

OEHHA appears unwilling to acknowledge that the DE epidemiological results are very weak. The "rules of thumb" about weak RR's that OEHHA appears to reject (Page C-OEHHA-18), appear to be accepted by other authoritative bodies. The WHO (1980) advises:

"The strength of the association relates to causality. Relative risks of less than 2.0 may readily reflect some unperceived bias or confounding factor, those over 5.0 are unlikely to do so." (WHO, 1980, p. 36).

The National Cancer Institute (NCI) has commented on weak RR's, noting that:

"In epidemiological research, relative risks of less than 2 are considered small and are usually difficult to interpret. Such increases may be due to chance, statistical bias, or effects of confounding factors that are sometimes not evident." (NCI, 1994)

6.2 Missing Caveats on OEHHA's Treatment of the Mice Data

When discussing the carcinogenicity of diesel exhaust in mice, both in the summary Section 1.3.1 and in the detailed Section 6.1.1.1, OEHHA fails to point out the weaknesses of the data in mice that they claim support carcinogenicity of diesel exhaust. OEHHA refers to the tumor data in mouse studies as being "*mixed*" (Executive Summary pp 21; Part B, pp 1-5, 6-1). This conclusion does not reflect the conclusions of the authors of the studies cited.

Numerous inhalation studies (Pepelko and Peirano, 1983; Heinrich *et al.*, 1986; Takemoto *et al.*, 1986; Heinrich *et al.*, 1995; Mauderly *et al.* 1996) have been conducted using different strains of mice; Pepelko and Peirano (1983) and Heinrich *et al.* (1986) are the only **two** inhalation studies reporting positive findings. It is a serious omission that the agency does not mention shortcomings that would affect the interpretation of these two "*positive*" studies.

(1) Pepelko and Peirano (1983)

The results of the various experiments are noted in OEHHA's text and in OEHHA Tables 6.1.b. and 6.2.b., but the agency only acknowledges the importance of the positive findings, and minimizes any shortcomings (pathology assessment, exposure duration, premature sacrifices) and minimizes negative findings.

- None of the experiments used lifetime exposures. In only one experiment (male and female offspring of Sencar mice) were the exposures continued beyond 12 months of age.
- All of the experiments terminated the animals before they reached the end of their natural lifespan. In the cases of strains (such as those used in this study) that have a high spontaneous tumor incidence, premature sacrifice could affect comparisons between control and exposed animals.
- For those experiments in strain A mice (Jackson A and Strong A) gross examination, not histologic examination, of the lungs was used to assay for lung tumors. The authors did not indicate whether the pathologists were blind to exposure group.
- Increases in lung tumors were observed in female Strong A mice (6 mg/m³) and female Sencar mice (6 mg/m³ + 12 mg/m³), but **no** increases in lung tumors were found in male Strong A mice (6 mg/m³, 12 mg/m³), female Strong A mice (12 mg/m³), male Sencar mice (6 mg/m³ + 12 mg/m³), and male Jackson A mice (6 mg/m³ or 12 mg/m³).

- With respect to the positive finding in the female Strong A mice, OEHHA failed to acknowledge the following statement made by the authors:

*"In this study, females exposed to exhaust (6 mg/m³ particulate) or exhaust plus urethan showed a slight, but significant, increase in tumor counts when compared to their respective controls. This slight positive response **can probably be discounted for several reasons**. [emphasis added] First, the control levels in that particular study were less than the expected value of about 0.25 tumors/mouse. If the historic value of 0.25 tumors/mouse is used, then a significant increase cannot be detected. Secondly, according to Shimkin and Stoner (1975), unless the tumor incidence exceeds 1 per mouse, the increase should not be considered significant. Finally, we were not able to confirm the increase even at a higher level of exposure."* (Pepelko and Peirano, 1983, page 274)

- With respect to the study with Sencar mice, the investigators exposed a parent generation of mice to 6 mg/m³ diesel exhaust. The exposure continued during mating and pregnancy, and then the offspring were exposed until 15 months of age. At approximately 12 weeks of age the concentration of diesel exhaust was raised to 12 mg/m³. Subgroups of animals received interperitoneal injections of the tumor promoter, urethan, or the tumor initiator, butylated hydroxytoluene (BHT). Of all the possible comparisons (treatment: untreated, urethan, BHT; gender: male, female; tumor type: benign, malignant), diesel exhaust exposure only increased the adenoma incidence in untreated female mice. Furthermore, diesel exhaust decreased adenoma incidence in BHT-treated female mice. All other comparisons revealed no effect of diesel exposure. OEHHA failed to acknowledge the following statement made by the authors:

*"Thus, while exposure to DE did appear to induce lung tumors in certain instances" [actually, only one instance, adenomas in untreated female mice], "the results were of **insufficient consistency to draw conclusions** [emphasis added]."* (Pepelko and Peirano, 1983, page 278)

- Two of the experiments (male Jackson A exposed to 12 mg/m³, female Strong A mice exposed to 12 mg/m³) reported a **decrease** in lung tumor incidence with diesel exposure. One could argue that OEHHA should have concluded that exposures to high concentrations of diesel exhaust is **protective** for mice! In fact, OEHHA needs to acknowledge the common finding that some "chemical carcinogens" increase the incidence of one type of tumor, but decrease the incidence of another, or increase the tumor incidence in one species while decreasing it in another (Davies and Monro, 1994).

(2) Heinrich *et al.* (1986)

Heinrich *et al.* reported an increase in lung tumor incidence for diesel exposed mice (control = 13%, whole diesel exhaust = 32%, and filtered diesel exhaust = 31%). However, the authors also noted the abnormally low spontaneous tumor incidence in the control animals (that is, 13%), which for the NMRI strain is usually around 30%. The low tumor incidence in the control animals thus created a statistically significant difference between the control animals and the diesel-exposed animals. OEHHA

neglects to mention this important caveat. A later replication of this work (Heinrich *et al.* 1995) study using NMRI mice was negative and the spontaneous tumor incidence was around the expected 30%. As noted by the HEI,

"The data from Heinrich and colleagues (1986) in female NMRI mice may now be interpreted as negative in view of the more recent studies with the same mouse strain at higher concentrations of diesel exhaust (Heinrich et al., 1995)" (Busby and Newberne, HEI report, 1995)

The two studies in mice by Heinrich *et al.* (1995) and Mauderly *et al.* (1996) were designed as carcinogenicity bioassays. Large numbers of animals of both genders were exposed to multiple levels of diesel exhaust over their lifetime. Three strains of mice (NMRI, C57BL/6N, and CD-1) with different spontaneous tumor rates were evaluated. Assessment was extensive, including microscopic examination. Neither of these extensive investigations reported an increase in lung tumor incidence.

OEHHA needs to correct its inaccurate and incomplete presentation of the mice results as being "mixed" by including the above excerpts of the cited researchers' own words.

6.3 Bioavailability of Diesel-Exhaust PAH is Not Well Supported

In the Executive Summary, CARB/OEHHA summarizes data on the bioavailability of genotoxic substances on diesel particles. Using four lines of reasoning the agency concluded,

"Consequently, it appears that organic chemicals adsorbed onto the particles, particularly the genotoxic components, are likely to be bioavailable to humans." (ES-19)

The rationale behind this conclusion comes from CARB/OEHHA's unbalanced interpretation of the scientific evidence.

The four arguments presented by CARB/OEHHA, and their flaws are as follows:

"First, the in vitro genotoxic activity of diesel exhaust particulate dispersed in pulmonary surfactant exhibited similar activity to extracts of diesel exhaust particles." (ES-19)

It appears from the wording of this statement, that OEHHA is relying on the studies by Wallace *et al.* (1987) and Keene *et al.* (1991), who demonstrated an increase in mutagenicity after incubation of diesel-exhaust particles with a phospholipid emulsion. After incubation with the emulsion, the investigators separated the particles from the media and observed that the mutagenicity resided with the particulate fraction and not with the filtered supernatant. That is, the emulsion was not effective in extracting the organic material off the diesel particles. The relevance of this test system, or any other extraction test system, to the *in vivo* situation remains to be validated. For example, at an average total air exposure concentration of 1.5 $\mu\text{g}/\text{m}^3$, the lungs are not under overload, and macrophages are not impaired in their ability to take up and remove particles. As noted earlier in our Section 2.3, we estimate

that there are 200-600 resident alveolar macrophages for each particle that is deposited daily in the alveolar region of the lung, at inhaled particle concentrations of $1.5 \mu\text{g}/\text{m}^3$.

"Second, inhalation exposure of rats and monkeys to diesel exhaust results in DNA adduct formation and in vitro exposures of rat tissues to diesel exhaust induces unscheduled DNA synthesis." (ES-19)

With respect to OEHHA relying on some of the earlier studies by Bond and coworkers, it is important to note that these investigators measured total DNA adducts in diesel-exposed rats. These exposures were such that the rats were experiencing lung overload. The investigators did not use methodology that would enable them to differentiate between adducts formed from oxidants and adducts formed from PAH or nitro-PAH exposures. In fact, exposure of rats to carbon black (Bond *et al.*, 1990) resulted in similar levels of adducts as with exposure to diesel exhaust, and the authors noted the possibility of inflammatory-based adduct formation.

Gallagher *et al.*, (1994) exposed rats to filtered air, diesel exhaust ($7.5 \text{ mg}/\text{m}^3$), carbon black ($11.3 \text{ mg}/\text{m}^3$), or titanium dioxide ($10.4 \text{ mg}/\text{m}^3$) for 2 years, then measured DNA adducts using different ^{32}P -postlabeling assays to differentiate among adduct types. The three particle-exposure groups had similar adduct profiles except for adduct 2, which was a nitro-PAH-derived DNA adduct. This adduct was observed in the diesel-exposed rats and in the sham-exposed rats (see Figures 3 and 4 in the article by Gallagher *et al.*, 1994).

"Third, DNA adducts have been associated with occupational exposure to diesel exhaust."(ES-19)

OEHHA reviewed the studies by Hemminki *et al.* (1994), Hou *et al.* (1995), and Nielsen *et al.* (1996), who investigated DNA adduct levels in peripheral blood cells from healthy, non-smoking males. The subjects were employed as bus garage workers, bus mechanics, or truck terminal workers in Sweden. In response to public comment, OEHHA acknowledged that information on diesel exhaust exposure was not available for these studies and that dermal exposure to diesel fuel and lubricating oil could exist. These extremely important caveats, which severely limit implicating diesel-engine exhaust as the source, must be included in any summary of this topic.

"Fourth, urinary metabolites of PAH's have been found following exposure of rats to diesel exhaust. Preliminary evidence indicates the same may be true for humans." (ES-19)

The basis for this statement appears to come from the studies by Kanoh *et al.* (1993) and by Scheeper *et al.* (1994). In the public comment, problems with these studies were brought to OEHHA's attention, which they have not as yet addressed.

Kanoh *et al.* (1993) conducted a short-term rat study to assess the use of urinary 1-hydroxypyrene as a marker of PAH exposure. For the calculation of inhaled PAH, the authors used airborne concentration of diesel particulate and not the deposition fraction. Therefore, pyrene values for inhalation should be 12% to 20% of 24.77 ng, that is, only 3 to 5 ng. For the calculation of ingested PAH, the authors implied that the two groups of rats consumed the same amount of food, but it does not appear that the authors measured food consumption. OEHHA only responded to the concerns about

whether food consumption could have increased in a compensatory manner after particle exposures ended. The fact remains, that there are **no** measures of food consumption. Furthermore, even if food consumption did not increase, and even if all the pyrene adsorbed to diesel particles were bioavailable, diesel exhaust-derived pyrene only accounted for about 2-3 % of the daily pyrene dose.

Scheeper *et al.* (1994) measured the concentration of urinary 1-aminopyrene in 3 diesel train-engine mechanics and 2 office clerks. OEHHA only reported the positive association between the mechanics and office clerks when days are combined. OEHHA did **not** report the following facts that do not support their conclusion. That is:

1. There were no differences between the two groups of employees when the authors compared daily excretion levels on a single-day basis.
2. A significant portion (approximately 70%) of the airborne particulate matter was not primarily derived from diesel exhaust.
3. Total suspended particulate matter (TSPM) and respirable suspended particulate matter (RSPM) levels were not consistent with the time and frequency of engine test runs.
4. In the mechanics, the highest 24-hour average of urinary 1-aminopyrene occurred on Monday, but airborne levels of 1-nitropyrene were not detectable, and finally,
5. The authors provide no information on other sources of nitro-PAHs to which mechanics may have been exposed.

The authors cautioned that this was a preliminary study, and should be treated as such when drawing conclusions about bioavailability; a caution, which OEHHA apparently missed.

Finally, Schenker *et al.* (1990) showed that urinary mutagenicity was not correlated with exposure to diesel exhaust in 87 railroad workers. The authors obtained measurements of RSP, using personal monitors, and corrected these values for exposure to environmental tobacco smoke. Although OEHHA does acknowledge that this study exists, its negative results are never entered as evidence.

Therefore, OEHHA's conclusion about the presence of urinary PAH's from diesel-exhaust exposure is **not** supported by the data and should not be used as evidence of bioavailability.

DE portion of $PM_{2.5}$ is deserving of a classification as a "Toxic Air Contaminant" while the other 92.5% is neglected. OEHHA uses the rat response to provide plausibility for the tumorigenic effect of DE particulate; however, rats also develop tumors from a large variety of solid particles, without regard to particle chemistry. Thus, the other 92.5% of $PM_{2.5}$ warrants classification as a TAC by the same rationale of the rat studies that OEHHA applies to DE.

In Appendix B, OEHHA reviews the concerns about ambient particulate generally. In terms of California being able to achieve the new NAAQS for $PM_{2.5}$, it would seem logical to focus OEHHA's energies on the sources comprising the other 92.5% of $PM_{2.5}$ ambient levels. Although Appendix B states that it is "*worthwhile to consider all major sources of PM,*" the reason for the intense focus on DE is not explained.

6.4 What is "Diesel Exhaust?"

In order to provide the public with a perspective on the issue under consideration, it is also essential that the Executive Summary provide some rationale for singling out diesel exhaust from emissions due to other sources. In particular, the document must answer the question of how diesel exhaust deserves classification separate from other fossil-fuel and renewable bio-fuel combustion sources. Within California, combustion soot from gasoline, home heating oil, coal, charcoal, tobacco smoke, wood, and cooking of food is ubiquitous. The pie chart on ES-8 should be supplemented with a pie chart similar to those on pages A-31 of the "Exposure Assessment" that clearly show that diesel exhaust represents 3% of all PM₁₀ sources in California, and 7.6% of all PM_{2.5} sources in California. PM_{2.5}.

The Executive Summary invites a dramatic misunderstanding of the issue of diesel exhaust composition by OEHHA's Figure shown on page ES-5, which comes directly under the heading "What is Diesel Exhaust?" and depicts diesel exhaust being exclusively composed of "solid carbon particles," "soluble organic fraction," and "gaseous hydrocarbons." At the very least, the Executive Summary should display, either in bar chart or pie chart form, the major constituents of diesel exhaust, and their relative proportions. Even the more detailed figures found on pages A-10 and A-11 of the "Exposure Assessment" report do not reflect the fact that the majority of the material coming out of the exhaust pipe of a diesel vehicle consists of nitrogen, oxygen, carbon dioxide, and water.

In order to accurately inform policymakers and the public, it is essential that OEHHA incorporate information that can be found in the WHO document on diesel exhaust (WHO, 1996). As can be seen from Table 2.1 (page 101) of the WHO document, 99.9 percent of diesel exhaust consists of nitrogen, oxygen, carbon dioxide, and water.

The hydrocarbon fraction of whole, undiluted diesel exhaust is only **7 parts per million** (by weight) (WHO, 1996). Moreover, the particulate matter in whole, undiluted diesel exhaust is 60 parts per million; the PAH content of the particulate matter (Table 2.3, page 105 of the WHO document) ranges from units to hundreds of **parts per million**. Therefore, overall, the PAH content of whole **undiluted** diesel exhaust is of the order of and below **0.01 part per million**.

What the California public and California policymakers also need to know is that for the 1.5 µg/m³ diesel exhaust particulate concentrations to which they are exposed, the concentrations of PAHs are less than 0.0001 µg/m³. For an individual breathing 20 m³ per day, **this corresponds to a daily intake of 0.002 µg/day. This is far below the background intake levels of PAHs, which range from 2 to 20 µg/day** (ATSDR, 1994). Likewise, nitro-PAHs are also found in food (Dennis *et al.*, 1984). Everyday activities are likely to involve intake of "carcinogenic" chemicals. For example, barbecued meat contains elevated levels of carcinogenic nitrosamines (Kinouchi *et al.*, 1986). OEHHA needs to establish which, if any, of the PAHs or nitro-PAHs in the 1.5 µg/m³ DE particulate yields a level of intake above background.

The CARB document shows that of all sources of PM_{2.5}, diesel exhaust particulate contribute a total of 7.5% to PM_{2.5} levels. OEHHA needs to explain to policymakers and the public why the small

7 References

- Agency for Toxic Substances and Disease Registry (ATSDR). 1993. Polycyclic Aromatic Hydrocarbons (PAHs). U.S. Department of Health and Human Services.
- Ahlman, K., Koskela, R.S., Kuilla, P., Koponen, M., and Annanmaki, M. 1991. Mortality among sulfide ore miners. *Am J Ind Med* 19:603-617.
- Ambs, J.L., Cantrell, B.K., Watts, W.F., Olson, K.S. 1994. Evaluation of a disposable diesel exhaust filter for permissible mining machines. RI 9508. Bureau of Mines, Pittsburgh, PA.
- Austin, A.C., Claxton, L.D., and Lewtas, J. 1985. Mutagenicity of the fractionated organic emissions from diesel, cigarette smoke condensate, coke oven, and roofing tar in the Ames assay. *Environ. Mutagen.* 7:471-487.
- Bagley, S.T., Baumgard, K.J., Gratz, L.D., Johnson, J.H., and Leddy, D.G. 1996. Characterization of fuel and aftertreatment device effects on diesel emissions. Health Effects Institute Reserach Report No. 76. Cambridge, MA.
- Bhatia, R., Lopipero, P., and Smith, A.H. 1998. Diesel exhaust exposure and lung cancer. *Epidemiology* 9:84-91.
- Blome, H., Heidermanns, G., and Timmer, L. 1990. [Assessment of workplace atmosphere in case of diesel motor vehicles.] *Stab Reinhalt Luft* 50:93-97 (in German).
- Boffetta, P., Stellman, S.D., and Garfinkel, L. 1988. Diesel exhaust exposure and mortality among males in the American Cancer Society prospective study. *Am J Ind Med* 14:403-415.
- Bond, J.A., Johnson, N.F., Snipes, M.B., and Mauderly, J.L. 1990. DNA adduct formation in rat alveolar Type II cells: Cells potentially at risk for inhaled diesel exhaust. *Environ. Mole. Mut.* 16:64-69.
- Cohen, A., and Higgins, M. 1995. Health effects of diesel exhaust: Epidemiology. In *Diesel Exhaust: A Critical Analysis of Emission, Exposure, and Health Effects* (Health Effects Institute Diesel Working Group). Health Effects Institute, Cambridge, MA.
- Cox, LA. 1997. Does diesel exhaust cause human lung cancer? *Risk Analysis* 17:807-829.
- Culotta, E., and Koshland, D.E. 1994. DNA repair works its way to the top. *Science* 266:1926-1929.
- Davies, T.S.; Monro, A. 1995. The rodent carcinogenicity bioassay produces a similar frequency of tumor increases and decreases: Implications for risk assessment. *Reg. Tox. Pharmacol.* 20:281-301.

- Dennis, M.J., Massey, R.C., McWeeny, D.J., Knowles, M.E. 1984. Estimation of nitropolycyclic aromatic hydrocarbons in foods. *Food Addit. Contam.* 1:29-37.
- Emmelin, A., Nystrom, L., and Wall S. 1993. Diesel exhaust exposure and smoking: A case-referent study of lung cancer among Swedish dock workers. *Epidemiology* 4:237-244.
- Gallagher, J., Heinrich, U., George, M., Hendee, L., Phillips, D.H., and Lewtas, J. 1994. Formation of DNA adducts in rat lung following chronic inhalation of diesel emissions, carbon black, and titanium dioxide particles. *Carcinogen.* 7:1293-1299.
- Gamble, J., Jones, W. and Minshall, S. 1987. Epidemiological-environmental study of diesel bus garage workers: Acute effects of NO₂ and respirable particulate on the respiratory system. *Environ Res* 42:201-214.
- Garshick, E., Schenker, M.B., Munoz, A., Segal, M., Smith, T.J., Woskie, S.R., Hammond, K.S., and Speizer, F.E. 1987. A case-control study of lung cancer and diesel exhaust exposure in railroad workers. *Am Rev Respir Dis* 135:1242-1248.
- Garshick, E., Schenker, M.B., Munoz, A., Segal, M., Smith, T.J., Woskie, S.R., Hammond, K.S., and Speizer, F.E. 1988. A retrospective cohort study of lung cancer and diesel exhaust exposure in railroad workers. *Am Rev Resp Dis* 137:820-825.
- Gustafsson, L., Wall, S., Larsson L-G., and Skog, B. 1986. Mortality and cancer incidence among Swedish dock workers-A retrospective cohort study. *Scand J Work Environ Health* 12:22-26
- Gustafsson, L., Plato, N., Lidstrom, E-B., and Hogstedt. 1990. Lung cancer and exposure to diesel exhaust among bus garage workers. *Scand J Work Environ Health* 16:348-354.
- Hansen, E.S. 1993. A follow-up study on the mortality of truck drivers. *Am J Ind Med* 23:811-821.
- Hayes, R.B., Thomas, T., Silverman, D.T., Vineis, P., Blot, W.J., Mason, T.J., Pickle, L.W., Correa, P., Fontham, E.T.H., and Schoenberg, J.B. 1989. Lung Cancer in motor-exhaust related occupations. *Am J Ind Med* 16:685-695.
- Heinrich, U., Fuhst, R., Rittinghausen, S., Creutzenberg, O., Bellmann, B., Koch, W., and Levsen, K. 1995. Chronic inhalation exposure of Wister rats, and two different strain of mice to diesel engine exhaust, carbon black and titanium dioxide. *Inhal. Toxicol.* 7:533-556.
- Heinrich, U., Muhle, H., Takenaka, S., Ernst, H., Fuhst, R., Mohr, U., Pott, F., and Stöber, W. 1986. Chronic effects on the respiratory tract of hamsters, mice and rats after long-term inhalation of high concentrations of filtered and unfiltered diesel engine emissions. *J. Appl. Toxicol.* 6:383-395.
- Hemminki, K., J. Soderling, P. Ericson, H.E. Norbeck, and Segerback, D. 1994. DNA adducts among personnel servicing and loading diesel vehicles. *Carcinogen.* 15:767-769.

- Hinds, W., First, M.W., Huber, G.L., and Shea, J.W. 1983. A method for measuring respiratory deposition of cigarette smoke during smoking. *Am. Ind. Hyg. Assoc. J.* 44:113-118.
- Hou, S., B. Lambert, and Hemminki, K. 1995. Relationship between hprt mutant frequency, aromatic DNA adducts and genotypes for GSTM1 and NAT2 in bus maintenance workers. *Carcinogen.* 16:1913-1917.
- Howe, G.R., Fraser, D., Lindsay, J., Presnal, B., and Y.S. Zhang. 1983. Cancer mortality (1965-77) in relation to diesel fume and coal exposure in a cohort of retired railway workers. *J Natl Canc Inst* 6:1015-1019.
- International Agency for Research on Cancer (IARC). 1980. Statistical Methods in Cancer Research. (N.E. Breslow, N.E. Day, Editors) Section 1.7, "Interpretation." IARC Scientific Publication No. 32, Lyon, France.
- Kanoh, T., M. Fukuda, H. Onozuka, T. Kinouchi, and Ohnishi, Y. 1993. Urinary 1-hydroxypyrene as a marker of exposure to polycyclic aromatic hydrocarbons in environment. *Environ. Res.* 62:230-241.
- Keane, M.J., S-G. Xing, J.C. Harrison, T. Ong, and Wallace, W.E. 1991. Genotoxicity of diesel-exhaust particles dispersed in simulated pulmonary surfactant. *Mut. Res.* 260:233-238.
- Kinouchi, T; Tsutsui, H.; Ohnishi, Y. 1986. Detection of 1-nitropyrene in yakitori (grilled chicken). *Mutation Research* 171:105-113.
- Lash TL, Crouch EAC, Green LC. 1997. A meta-analysis of the relation between cumulative exposure to asbestos and relative risk of lung cancer. *Occup. Environ. Med.* 54:254-263.
- Lee, PN. 1989. "4. Problems in Interpreting Epidemiologic Data," in Assessment of Inhalation Hazards (Eds.: D.V. Bates, D.L. Dungworth, P.N. Lee, R.O. McClellan, F.J.C. Roe) ILSI Monographs.
- Lerchen, M.L., Wiggins, C.L., and Samet, J.M. 1987. Lung cancer and occupation in new Mexico. *J Natl Cancer Inst* 79:639-645.
- Lewtas, J., Bradow, R.L., Jungers, R.H., Harris, B.D., Zweidinger, R.B., Cushing K.M., Gill, B.E., and Albert R.E. 1981. Mutagenic and carcinogenic potency of extracts of diesel and related environmental emissions: Study design, sample generation, collection, and preparation. *Environ. Internatl.* 5:383-387.
- Linet, M.S., Hatch, E.H. *et al.* 1997 Residential Exposure to Magnetic Fields and Acute Lymphoblastic Leukemia in Children *New England Journal of Medicine.* 337:1-7.
- Mauderly, J.L., D.A. Banas, W.C. Griffith, F.F. Hahn, R.F. Henderson, and R.O. McClellan. 1996. Diesel exhaust is not a pulmonary carcinogen in CD-1 mice exposed under conditions carcinogenic to F344 rats. *Fundam. Appl. Toxicol.* 30:233-242.
- Morgan WKC, Reger RB, Tucker DM. 1997. Health effects of diesel emissions. *Ann Occup Hygiene* 41:643-658.

- Muscat, J.E., and Wynder, E.L. 1995. Diesel engine exhaust and lung cancer: An unproven association. *Environ Health Perspect* 103:812-818.
- National Academy of Sciences (NAS). 1996. Possible Health Effects of Exposure to Residential Electric and Magnetic Fields. National Research Council, Committee on the Possible Effects of Electromagnetic Fields on Biologic Systems. National Academy of Sciences Press, Washington, DC.
- National Cancer Institute (NCI). 1994. Press Release on "Abortion and Possible Risks for Breast Cancer: Analysis and Inconsistencies." National Institutes of Health, Bethesda, MD, October 26, 1994.
- Nielsen, P.S., A. Andreassen, P.B. Farmer, S. Ovrebo, and Autrup, H. 1996. Biomonitoring of diesel exhaust-exposed workers: DNA and hemoglobin adducts and urinary 1-hydroxypyrene as markers of exposure. *Tox. Lett.* 86:27-37.
- Park RM, NA Maizlish, L Punnet, R Moure-Eraso, MA Silverman. 1991. A comparison of PMRs and SMRs as estimators of occupational mortality. *Epidemiology* 2:49-59.
- Pepelko, W.E., and Peirano, W.B. 1983. Health effects of exposure to diesel engine emissions: A summary of animal studies conducted by the U.S. Environmental Protection Agency's Health Effects Research Laboratories at Cincinnati, Ohio. *J. Am. Coll. Toxicol.* 2:253-306.
- Rushton, L., Alderson, M.R., and Nagarajah, C.R. 1983. Epidemiological survey of maintenance workers in London transport executive bus garages and Chiswick Works. *Br J Ind Med* 40:340-345.
- Scheepers, P.T.J., H.J.T.M. Thuis, M.H.J. Martins, and Bos, R.P. 1994. Assessment of occupational exposure to diesel exhaust. The use of an immunoassay for the determination of urinary metabolites of nitroarenes and polycyclic aromatic hydrocarbons. *Tox. Lett.* 72:191-198.
- Schenker, M.B. 1989. "27. Epidemiologic Studies of Populations Exposed to Motor Vehicle Exhausts and Polycyclic Aromatic Hydrocarbons." in Assessment of Inhalation Hazards (Eds.: D.V. Bates, D.L. Dungworth, P.N. Lee, R.O. McClellan, F.J.C. Roe) ILSI Monographs.
- Schenker, M.B. N.Y. Kado, S.K. Hammond, S.J. Samuels, S.R. Woskie, and Smith, T.J. 1992. Urinary mutagenic activity in workers exposed to diesel exhaust. *Environ. Res.* 57:133-148.
- Speizer FE. 1986. Overview of the risk of respiratory cancer from airborne contaminants. *Env. Health Perspec.* 70:9-15.
- Stober, W., and Abel, U.R. 1996. Lung cancer due to diesel soot particles in ambient air? A critical appraisal of epidemiological studies addressing this question. *Occup Environ Health* 68(S):3-61.
- Steele, R.H., Payne, V.M., Fulp, C.W., Rees, D.C., Lee, C.K., and Doolittle, D.J. 1995. A comparison of the mutagenicity of mainstream cigarette smoke condensates from a representative sample of the U.S. cigarette market with a Kentucky reference cigarette (K1R4F). *Mut. Res.* 342:179-190.

- Steenland, N.K., Silverman, D.T., and Hornung, R.W. 1990. Case-control study of lung cancer and truck driving in the Teamsters Union. *Am J Public Health* 80:670-674.
- Stober, W., and Abel, U.R. 1996. Lung cancer due to diesel soot particles in ambient air? A critical appraisal of epidemiological studies addressing this question. *Occup. Environ. Health* 68(suppl):S3-S61.
- Swanson, G.M., Lin, C-S., and Burns, P.B. 1993. Diversity in the association between occupation and lung cancer among black and white men. *Cancer Epidemiol Biomarkers Prev* 2:313-320.
- Takemoto, K., H. Yoshimura, and Katayama, H. 1986. Effects of chronic inhalation exposure to diesel exhaust on the development of lung tumors in di-isopropanol-nitrosamine-treated F344 rats and newborn C57BL and ICR mice. In: Carcinogenic and Mutagenic Effects of Diesel Engine Exhaust (Ishinishi N., Koizumi A., McClellan R.O., Stober W., eds.) pp. 311-327. Elsevier Science Publishing Co., New York, NY.
- Thun MJ, DG Myers, C Day-Lally, MM Namboodiri, EE Calle, WD Flanders, SL Adams, CW Heath. 1997. Age and the exposure-response relationships between cigarette smoking and premature death in the Cancer Prevention Study II. IN: Changes in Cigarette-Related Disease Risks and Their Implication for Prevention and Control. National Institutes of Health, Monograph 8 in the Smoking and Tobacco Control Series, National Cancer Institute. NIH Publication No. 97-4213, pp. 383-412.
- USEPA. 1996. Review of the National Ambient Air Quality Standards for Particulate Matter: Policy Assessment of Scientific and Technical Information. OAQPS Staff Paper. EPA/452/R-96-013. Office of Air Quality Planning and Standards, Research Triangle Park, NC. July, 1996 (See also alveolar deposition calculations in "Air Quality Criteria for Particulate Matter," Volume II of III, Chapter 10, page 10-167, Table 10-31, EPA/600/AP-95/001b.)
- USNIOSH. 1989. Health hazard evaluation report: Consolidated Freightways, Peru, Illinois. (NIOSH Report No. HHE HETA-88-077-1969). US Dept. of Health and Human Services, Cincinnati, OH.
- USNIOSH. 1990. Final report of the NIOSH health hazard evaluation conducted at Madison Metro's Transit System's Maintenance and Administration Facility, January 1989. (NIOSH Report No. HHE HETA-88-218). US Dept. of Health and Human Services, Cincinnati, OH. 38 pp.
- Wallace W.E., M.J. Keane, C.A. Hill, J. Xu, and Ong, T. 1987. Mutagenicity of diesel exhaust particles and oil shale particles dispersed in lecithin surfactant. *J. Toxicol. Environ. Health*. 21:163-171.
- Waller, R.E. 1981. Trends in lung cancer in London in relation to exposure to diesel fumes. *Environ Int* 5:479-483.
- Waller, R.E., Hampton, L., and Lawther, P.J. 1985. A further study of air pollution in diesel bus garages. *Br J Ind Med* 42:824-830.
- Walrath, J., Rogot, E., Murray, J, and Blair, A. 1985. Mortality patterns among US veterans by occupation and smoking status, Vol 1 (NIH Publication No. 85-2756). Washington D.C., US Government Printing Office.

Wong O., Morgan R.W., Kheifets, L., Larson, S.R., and Whorton, M.D. 1985. Mortality among members of a heavy construction equipment operators union with potential exposure to diesel exhaust emissions. *Br J Ind Med* 42:435-448.

World Health Organization (WHO). 1996. Diesel Fuel and Exhaust Emissions. Environmental Health Criteria 171, Geneva, WHO.

Woskie, S.R., Smith, T.J., Hammond, K., Schenker, M.B., Garshick, E., Speizer, F.E. 1988. Estimation of the diesel exhaust exposures of railroad workers: II. National and historical exposures. *Am J Ind Med* 13:395-404.

Yu C.P., and Xu, G.B. 1987. Predictive models for deposition of inhaled diesel exhaust particles in humans and laboratory species. Health Effects Institute Research Report No. 10, Cambridge, MA.

Zaebst, D.D., Clapp, D.E., Blade, L.M., Marlow, D.A., Steenland, K., Hornung, R.W., Scheutzle, D., and Butler, J. 1991. Quantitative determination of trucking industry workers' exposures to diesel exhaust particles. *Am Ind Hyg Assoc J* 52:529-541.

**COMMENTS ON OEHHA'S 2-98 DRAFT RISK
ASSESSMENT FOR DIESEL EXHAUST**

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INTRODUCTION AND SUMMARY

ARB/OEHHA recently (February 23rd, 1997) released its revised draft risk assessment and its staff responses to public comments received in 1997 on their previous Proposed Identification of Diesel Exhaust as a Toxic Air Contaminant. As in each previous draft, changes have been made in the arguments advanced in Part B: Health Risk Assessment for Diesel Exhaust. Among these are:

- The decision to base the final risk assessment numbers on epidemiological data only, rather than on rat data that many commenters consider inappropriate or irrelevant for low-dose risk assessment. We applaud this decision, while believing that the current "informational" analysis of rat data can and should be improved.
- New assumptions and assertions about shop worker exposures (see C-OEHHA-86).
- More accurate wording and removal of some of the potentially misleading statements about exposure uncertainties.

As in each previous draft, OEHHA has changed its assumptions without substantially changing its conclusions. Yet, many further changes, all previously identified in written comments but not yet addressed by OEHHA in their responses, are still needed to make the health risk assessment scientifically valid and statistically sound. Among the most important are the following:

- Causality: The current draft still fails to apply appropriate tests -- or, indeed, any formal statistical tests -- for causality. Yet, it flatly claims, and the Executive Summary states, that epidemiological data are "consistent with a causal relationship between occupational exposure to diesel exhaust and lung cancer" (ES-20). This crucial, policy-relevant claim is unwarranted by OEHHA's data analysis. Not a single statistical test of the hypothesis of causality has been performed or cited that would support it. [Indeed, in a new development, OEHHA is now claiming that no such tests exist (C-OEHHA-56), despite the fact that hundreds of highly reputable, widely cited papers, books, and monographs deal specifically with statistical tests of causal hypotheses.] The current draft presents OEHHA's assertion about causality as a fact-driven conclusion based on analysis of relevant data. But, as they concede that they have not tested the hypothesis, it is really no more than a statement of subjective staff opinions unsupported by appropriate tests or data analysis. Much recent literature contradicts OEHHA's opinion about causation. As just one example, Morgan *et al.* (1997) note that "Although there have been a number of papers suggesting that diesel fumes may act as carcinogens, the weight of the evidence is against this hypothesis." OEHHA's final conclusion is that "We believe that at current ambient concentrations, diesel exhaust may cause an increase in the likelihood of cancer. Therefore we conclude that diesel exhaust meets the

legal definition of a TAC..." (ES-26). Such an important belief should be subjected to formal testing using data before being accepted as a basis for policy making.

- **Misrepresented epidemiological evidence:** The most salient aspect of recent epidemiological studies, literature reviews, and meta-analyses of the causal relation between DE exposure and cancer risk is that *different reputable studies reach conflicting conclusions*. OEHHA's draft does not adequately convey this conflict. Instead, it suggests that multiple independent meta-analyses all reach broadly consistent conclusions. This misrepresents the sharply divided literature. The misrepresentation appears to be deliberate, given the many comments that OEHHA has received in the past about its one-sided reporting of relevant literature. It means that a policy maker or member of the public who wishes to make a well-informed, unbiased judgment about DE health risks cannot do so based on the current draft. The current draft is heavily biased by emphasizing sources that agree with its staff's opinions and omitting or minimizing sources that disagree.

- **Deliberate use of biased statistical models and methods:** In interpreting both rat and human data, OEHHA staff have knowingly used statistical models and methods that are biased to produce positive statistical associations between DE exposure and lung cancer risk even in the absence of any true relation. They then subjectively interpret these associations as evidence of a causal relation, while carefully avoiding making any statistical tests that could falsify this interpretation. Worse, they refuse to apply well developed and widely accepted statistical methods that would allow their assumptions about causality and risk to be tested objectively and that would avoid the biases needed to achieve positive statistical associations. Examples of deliberate biases in their analysis include:
 - Use of models that are incapable of showing effects at high doses but no effects at low doses, even when there are no effects at low doses.
 - Use of models that ignore exposure error.
 - Use of inconclusive qualitative criteria for judging causality
 - Improper characterization of uncertainty about risks (and the models on which risks are based)
 - Use of risk measures that always show higher risk in exposed compared to unexposed groups, even when the risks in both groups are identical.
 - Knowing acceptance and use of statistical methods that present false positives (i.e., associations due to chance) as being statistically significant associations.(i.e., not due to chance).
 - Presentation of confidence intervals that are artificially narrowed (by deliberate use of miscalculated p-values and exclusion of relevant uncertainties about the models and assumptions used) so that they will not include 1 (corresponding to zero elevated risk) as a possible value.

- Creation of new assumptions about exposure that will support OEHHA's previous position, even though the new and old assumptions are logically inconsistent – and avoidance of statistical models that would take into account uncertainties in these assumptions.

Each of these points is explained and documented in the pages that follow, using OEHHA's own words wherever possible. Together, they invalidate OEHHA's claim that current epidemiological evidence suggests or makes "very likely" (p. 6-59) a causal relation between DE exposure and human lung cancer risk.

COMMENTS AND QUESTIONS

OEHHA consistently portrays itself as having conducted a comprehensive, balanced, and reasonably accurate analysis (e.g., C-OEHHA-65) and suggests that its written responses to comments should be used to judge the quality of its process for incorporating public concerns. For example, they state:

"OEHHA responds to each substantive comment received from the public in Part C. These analyses and responses speak for themselves as to whether OEHHA positions are based upon 'sound scientific knowledge, methods, and practices'" (C-OEHHA-65).

In the following discussion, we accept the implicit invitation to use their current responses to public comments to assess the quality of OEHHA's basis for its positions. Unfortunately, as documented below, the current responses do not address most of our previously raised concerns. Instead, their responses to our previous comments consist largely of a mixture of

- *Straw-man arguments*, in which OEHHA substitutes a new concern for the one we expressed, and then replies to the new concern instead of to our comment.
- *Ignored comments*. Many of our past comments and requests (e.g., for clarification of what criteria OEHHA has used to determine that the Garshick *et al.* data are suitable for quantitative risk assessment) have not been responded to at all.
- *Non-responsive responses*. In several cases, OEHHA restates our concerns and then simply passes on or offers extraneous comments without addressing them.
- *Inaccurate responses*. OEHHA repeatedly characterizes its own work as comprehensive, unbiased, technically appropriate, and technically correct. We disagree. Specific examples of remaining errors and omissions follow.

Such debating tactics raise a meta-concern: that OEHHA may fail to ever recognize and respond to issues that we urgently believe compromise the validity of their analysis. They may succeed in using what we believe are flawed technical analyses, methods, and logic to persuade themselves, the public and decision-makers that DE exposure poses a real health threat that should be managed through further regulation, even though the opposite conclusion would emerge if they would stop and think through the logical and technical weaknesses in their analysis and honestly report the results. To try to reduce this risk, we have supplemented our comments with specific questions about their analysis and assumptions that we would like OEHHA to answer.

Since OEHHA has generally not addressed the concerns we have already submitted, the following section recapitulates them and reviews how OEHHA has responded or failed to respond to each one.

1. CONCERNS ABOUT CAUSALITY

In our 1997 comments, we raised the following concerns about causality.

Our original statements:

" OEHHA's causal interpretation of the relation between DE exposure and human lung cancer (Section 6.2.4) is unsupported by any formal statistical tests for causation. The reported associations are expected based solely on the statistical methods used, even if DE exposure has no effect on lung cancer. Thus, OEHHA's meta-analysis does not support the conclusion that DE exposure contributes to human lung cancer risk.

OEHHA's claim that 'Support for the finding of a carcinogenic effect of diesel exhaust also comes from the meta-analysis in Appendix D' (C-OEHHA-152) is not justified. The meta-analysis deals only with statistical associations, rather than with cause and effect. No statistical tests for causation have been performed (see Table 6). The individual studies cited by OEHHA in their meta-analysis suffer from the artifacts listed in Table 5, so that they are expected to produce false positives (and hence the appearance of a small but consistent pattern of elevated risks in exposed populations) even in the absence of a causal relation between them. Thus, observing such a pattern provides no evidence of a causal association between DE exposure and lung cancer." [The Tables 5 and 6 referenced provide guides to relevant literature on statistical tests for causation and a list of plausible non-causal explanations for observed associations between DE exposure and lung cancer.]

OEHHA's response: OEHHA (p. C-OEHHA-147 of 2-98 draft) responds as follows: "The commenter is correct in stating that the meta-analysis deals only with statistical associations and that no statistical tests for causation were

performed. Causal inference in chronic disease epidemiology involves an assessment of statistical associations, but requires an evaluation of a number of other factors as well, including (among others) the consistency of the findings among multiple studies, whether the findings are likely to be due to bias or chance, biological plausibility, and the existence of exposure-response relationships. These and other considerations are discussed at length in Section 6.2.4." Elsewhere (C-OEHHA-56, 2-98 draft) OEHHA states that "Contrary to any inference from the comment that OEHHA did not conduct 'a statistical test' for causality, statistical tests reveal associations, not causation. There is no *per se* statistical test for causation." Finally, in the Executive Summary (ES-20 of 2-98 draft), OEHHA states that "Based upon the epidemiological review and meta-analysis, these epidemiological studies provide evidence consistent with a causal relationship between occupational diesel exhaust exposure and lung cancer." Similarly, in Part B (p. 6-58 of 2-98 draft) they state that "The epidemiological studies concerning lung cancer risk and exposure to diesel exhaust provide evidence consistent with a causal relationship. The many associations found between lung cancer and diesel exposure are unlikely to be due to chance [and with some possible exceptions] are unlikely to be due to confounding or bias."

Rejoinder:

The following questions address various aspects of OEHHA's responses quoted above.

Q1. OEHHA concedes that "No statistical tests for causation were performed." Does OEHHA agree that it would be appropriate to perform such statistical tests for causation before claiming that their meta-analysis provides evidence "consistent with causation"?

Q2. We believe that it is inappropriate for OEHHA to state that "The epidemiological studies concerning lung cancer risk and exposure to diesel exhaust provide evidence consistent with a causal relationship" until they have formally tested this hypothesis and reported the results. Does OEHHA agree?

Q3. OEHHA states that "Statistical tests reveal associations, not causation. There is no *per se* statistical test for causation." We contend that, as indicated in Table 6 of our 1997 submission, there are many statistical tests for causation, based on several different principles outlined in our previous submission. For example, some of our own work (Cox, 1997) has used conditional independence tests of causation. (In these tests, a causal model or hypothesis such as "birth year → DE exposure → lung cancer risk" can be tested against an alternative causal hypothesis such as "DE exposure ← birth year → lung cancer risk" by checking whether lung cancer risk is *statistically independent* of DE exposure, given the value of birth year.) Such tests convinced us that the hypothesis that

DE exposure is a cause of increased lung cancer risk is not supported by the Garshick *et al.* data set.)

Among many useful references and surveys on statistical tests for causation, we have previously recommended the following to OEHHA:

Blalock, H.M., 1961. *Causal Inferences in Nonexperimental Research*. University of North Carolina Press, Chapel Hill.

Boudjellaba, H., J.-M. Dufour, and R. Roy, 1992. Testing causality between two vectors in multivariate autoregressive moving average models. *Journal of the American Statistical Association*, 87, 1082-1090.

Campbell, D.T., and J.C. Stanley, 1963. *Experimental and Quasi-Experimental Designs for Research*. Rand McNally, Chicago.

Cheeseman, P. and R.W. Olford (Eds.), 1994. *Selecting Models from Data*. Springer-Verlag, *Lecture Notes in Statistics*, Volume 89, pp. 339-350. New York.

Cohen, P.R., D.E. Gregory, L. Ballesteros, and R. S-Amant. Two algorithms for inducing structural equation models from data. Chapter 1 in D. Fisher and H-J Lenz (Eds), *Learning from Data: Artificial Intelligence and Statistics V*. Springer-Verlag, New York.

Ericsson, N.R., and J.S. Irons (eds), 1994. *Testing Exogeneity*. Oxford University Press, Oxford, England.

Geweke, J., 1984. Inference and Causality. Ch. 19 in Z. Griliches and M.D. Intriligator (Eds.), *Handbook of Econometrics*, Vol. 2. North-Holland, Amsterdam.

Granger, C.W.J., 1980. Tests for causation -- a personal viewpoint. *Journal of Economic Dynamics and Control*, 2, 329-52.

Granger, C.W.J., and P. Newbold, 1974. Spurious Regression in Econometrics. *Journal of Econometrics* 2 (2), 111-120.

Heise, D.R., 1975. *Causal Analysis*. Wiley, New York.

Hosoya, Y., "Causal analysis and statistical inference on possibly non-stationary time series." Chapter 1 in D.M. Kreps and K.F. Wallis (Eds), *Advances in Economics and Econometrics: Theory and Applications. Volume III*. Cambridge University Press, 1997.

Jensen, F.V. *An Introduction to Bayesian Networks*. Springer, 1996.

Kenny, D.A., 1979. *Correlation and Causality*. Wiley, New York.

Nelson, C.R. and G.W. Schwert, 1982. Tests for predictive relationships between time series variables. *Journal of the American Statistical Association*, 77, 11-18.

Pearl, J., 1996. A causal calculus for statistical research. Chapter 3 in D. Fisher and H-J Lenz (Eds), *Learning from Data: Artificial Intelligence and Statistics V*. Springer-Verlag, New York.

Shafer, G., 1996. *The Art of Causal Conjecture*. MIT Press. Cambridge, MA.

Simon, H.A., 1977. Causes and Possible Worlds. Section 2 in H.A. Simon, *Models of Discovery*. Dordrecht: D. Reidel.

Sims, C.A., Multivariate time series models. In J. Eatwell, M. Milgate, and P. Newman (Eds.) *The New Palgrave Time Series and Statistics*. W.W. Norton and Company. New York, 1990.

Swanson, N.R., and C.W.J. Granger, 1997. Impulse response functions based on a causal approach in residual orthogonalization in vector autoregressions. *Journal of the American Statistical Association*, **92**, 437, 357-367.

Yao, Q. and D. Tritchler, 1996. Likelihood-based causal inference. Chapter 4 in D. Fisher and H-J Lenz (Eds), *Learning from Data: Artificial Intelligence and Statistics V*. Springer-Verlag, New York.

We have previously provided these and other references on testing for causation to OEHHA, who appears to have ignored them. So, our questions are as follows:

Q3.1 *On what basis does OEHHA claim that "Per se statistical tests of causation do not exist"?*

Q3.2 *Did OEHHA review the references that we provided, or at least some references in each of the major categories of statistical tests for causation that we identified for them? If so, which ones do they consider most appropriate for testing the hypothesis that DE exposure causes increased risk of lung cancer? Specifically, do they prefer other methods to the conditional independence tests we have used?*

Q3.3 *Does OEHHA agree that its is appropriate to apply statistical tests of causation before reporting that data are consistent with a hypothesis of a causal relationship?*

Q3.4 *Does OEHHA agree that its conclusions about causation are not derived from objective statistical analyses of the data using appropriate tests that can be independently reproduced and verified?*

Q3.5 *OEHHA says of its responses to public comments that "These analyses and responses speak for themselves as to whether OEHHA positions are based upon 'sound scientific knowledge, methods, and practices'." (C-OEHHA-65). Does OEHHA agree that, in characterizing statistical tests for causation as "non-existent", their response does not adequately describe the state of relevant "scientific knowledge, methods, and practices" related to formal tests for causation?*

Q4: OEHHA states that "The epidemiological studies concerning lung cancer risk and exposure to diesel exhaust provide evidence consistent with a causal relationship".

Q4.1 *What specific, independently reproducible, quantitative criteria has OEHHA used to determine that the evidence is "consistent with a causal relationship?" (We have attempted to verify this claim, but find that the available evidence is consistent with non-causal interpretations rather than with causal ones, as documented in Cox, 1997).*

Q4.2 *Does OEHHA agree that the evidence from epidemiological studies is also consistent with absence of a causal relationship? In other words, do they agree that the epidemiological evidence could have arisen in the absence of a cause-and-effect relation? (The background for this question is that we have previously provided OEHHA with a list of specific non-causal explanations for observed statistical associations between DE exposure and lung cancer, namely, Table 5 of our 1997 submission. We believe that the observed pattern of associations reported in some meta-analyses is fully explained by multiple hypothesis testing bias, model selection bias, and other biases discussed in our previous submissions and discussed again later in this submission. Therefore, we believe that the epidemiological studies do not provide evidence for a causal relationship, but only evidence of statistical associations. We now ask OEHHA whether they agree that the observed patterns of association could result from non-causal sources. We believe that non-causal explanations are far more plausible than causal ones, and that they explain patterns, such as the fact that very differently exposed populations have very similar relative risks of lung cancer, that that would be difficult to explain if the patterns were causal.)*

Q5. OEHHA states that "Causal inference in chronic disease epidemiology involves an assessment of statistical associations, but requires an evaluation of a number of other factors as well, including (among others) the consistency of the findings among multiple studies, whether the findings are likely to be due to bias or chance, biological plausibility, and the existence of exposure-response relationships." By "evaluation" in this sentence, does OEHHA mean "subjective evaluation"? If not, what formal evaluation criteria does OEHHA endorse for each of the criteria listed? (The motivation for this question is that we believe that the DE exposure-lung cancer link fails on each of the criteria that OEHHA mentions here, as discussed next. To formally prove this, however, we would like to use a set of formal evaluation criteria that OEHHA agrees are appropriate.)

Q6: OEHHA states (p. 6-52) that "The following criteria for causal inference are considered: (1) the consistency of the findings; (2) the strength of the associations; (3) the possibility that findings are due to bias; (4) the likelihood that findings are due to chance; (5) evidence for exposure-response

relationships; (6) temporality of the associations; and (7) biological plausibility of a causal association.

Q6.1 Does OEHHA agree that the criteria they have listed are neither necessary nor sufficient for establishing causality?

Q6.2 Does OEHHA agree that conditional independence of the hypothesized cause and effect after adjusting for other factors (e.g., statistical independence of lung cancer risk from DE exposure after conditioning on age and other relevant factors) should be a sufficient criterion for rejecting the hypothesis of causality? [This is what we have observed in Cox (1997).]

Q6.3 Does OEHHA agree that if the hypothesized cause and effect are statistically significantly associated with each other (rather than being conditionally independent of each other) after conditioning on all other factors, then this should be a criterion for accepting the hypothesis of causality?

Q6.4 Is OEHHA willing to add conditional independence tests of causal hypotheses to its list of "criteria for causal inference"?

Q6.5 OEHHA claims (C-OEHHA-64) that "OEHHA assessed causal inference using standard criteria. These criteria included (1) the consistency of the findings; (2) the strength of the associations; (3) the possibility that findings are due to bias; (4) the probability that findings are due to chance; (5) evidence for exposure-response relationships; (6) temporality of the associations; and (7) biological plausibility of a causal association."

Q6.5.1 Does OEHHA agree that specificity of association is usually considered as part of this same set of "standard criteria" (e.g., Surgeon General's Report, 1964)?

Q6.5.2 Does OEHHA agree that the DE-lung cancer link fails the test of specificity?

Q6.5.3 On what grounds has OEHHA excluded mention of specificity from their list of "standard criteria"?

Q6.6 OEHHA's proposed set of "standard criteria" for causal inference is one of several such sets of criteria that have been proposed. As we have previously commented to OEHHA, it has been found not to work as well as hoped in epidemiology in clarifying issues of causation (Breslow, N.E., 1996. Statistics in Epidemiology: The Case Control Study. *Journal of the American Statistical Association* 91, 433, 14-28.) We therefore believe that another set of standard criteria for assessing validity of causal inferences, drawn from a different literature that we deem to be highly relevant, is more likely to be useful here. It consists of "History, maturation, testing, instrumentation, regression, selection, differential mortality, and interactions" (Campbell and Stanley, 1963). We

believe that the consistent statistical associations cited in the meta-analyses by OEHHA/Bhatia *et al.* as being consistent with or supportive of a causal interpretation fail on many of these alternative criteria (Cox, 1997).

Q6.5.1 *Does OEHHA agree that the criteria of history, maturation, testing, instrumentation, regression, selection, differential mortality, and interactions are appropriate and relevant for assessing the validity of causal inferences about DE exposure and lung cancer risk?*

Q6.5.2 *Does OEHHA agree that these criteria are also standard and widely accepted in a large literature on causal inference?*

Q6.5.3 *Does OEHHA agree that past epidemiological studies of DE exposure and lung cancer fail to support valid inferences of causality, as assessed by the criteria of history, maturation, testing, instrumentation, regression, selection, differential mortality, and interactions? (We have given specific examples of how some of these criteria can be applied in Cox, 1997, and found that past studies, specifically those of Garshick *et al.*, do not pass these tests for causality.)*

Q7. Consistency of findings: OEHHA states (p. 6-52) 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."

Q7.1 *Does OEHHA agree that consistently positive associations in multiple epidemiological studies could result from consistent use of models and data analysis methods that do not adequately protect against false positives?*

Q7.2 *Does OEHHA agree that consistently positive associations in multiple studies can be produced by any of several non-causal explanations, as previously suggested in our 1997 submission (e.g., Table 5 of our 1997 submission?)*

Q7.3 *More generally, does OEHHA agree that consistent positive associations are not by themselves evidence of causality and should not be considered evidence favoring causal explanations over non-causal explanations?*

Q7.4 We follow a large literature in statistics and philosophy of science (e.g., Campbell and Stanley, 1963) in accepting absence of a consistent positive association as evidence against a causal relation, while insisting that presence of a consistent positive association only justifies inference about associations, and not inference about causation, unless competing non-causal explanations (e.g., history, maturation, testing, instrumentation, regression, selection, differential mortality, and interactions) have been formally tested and ruled out. *Does*

OEHHA agree that presence of a consistent positive association only justifies inference about associations, and not inference about causation?

Q7.5 Some studies mentioned by OEHHA in their summary table (e.g., Kaplan 1959; Waller 1981; Bender et al., 1988) have reported statistically significantly negative associations between DE exposure and lung cancer risk. *Does OEHHA agree that such findings cast doubt on the accuracy of the significance levels and confidence intervals for relative risks reported in the literature?* (The background for this question is that we believe that the pattern of generally positive associations in the literature reflects statistical artifacts, such as improper calculation of p-values, that tend to create a large number of false positives being misconstrued as evidence of a true effect. This concern is described more fully later.)

Q8. OEHHA states (p. 6-52) that "Another recently published meta-analysis of diesel exhaust exposure and lung cancer found a similar consistency supportive of a causal relationship (Bhatia et al., 1998)."

Q8.1 *Why does OEHHA refer to the study of Bhatia et al. as "another" recently published meta-analysis?* (It is co-authored by Dr. A.H. Smith, who is also listed as an author of the OEHHA report. Its approach, methods,, results, and discussion closely overlap with those in the OEHHA report.)

Q8.2 *On what grounds does OEHHA characterize the consistency in studies that they and their colleagues Bhattia et al. have cited as "supportive of a causal relationship?" Please list any specific objective, independently reproducible criteria used to make this determination.* We believe that all of our technical concerns about OEHHA's analysis and conclusions apply equally to the paper of Bhatia et al, since the latter substantially follows OEHHA's approach, methods, interpretations, and conclusions. Specifically, Bhatia et al. claim in their abstract that "The meta-analysis supports a causal association", but do not justify this assertion anywhere in their text. Like OEHHA, they present no tests of causality to bolster their conclusion, which thus amounts to a statement of unsupported opinion. Like OEHHA, they point out that risk estimates are consistently above one (which does not favor causal over non-causal explanations, as discussed in Q7 above) and repeat OEHHA's claims that chance, as well as smoking, is unlikely to explain this pattern (which we disagree with for reasons given below,, and which leave other non-causal explanations unaddressed). But the sole sentence referring to "causal association" in their discussion is as follows. "The possible causal association between exposure to diesel exhaust and lung cancer is an important public health question." We do not believe that this qualifies as a demonstration that the associations are "supportive of a causal association". Does OEHHA have some other part of the Bhatia et al. paper in mind in making this characterization?

Q8.3 In the same issue of *Epidemiology* as Bhatia *et al.*, Dr. Debra Silverman of NCI comments that "Bhatia *et al.* conclude that the data support a causal association between diesel exhaust and lung cancer in humans. Has science proven causality beyond reasonable doubt? Probably not. The repeated finding of small effects, coupled with the absence of quantitative data on historical exposure, precludes a causal interpretation. To establish causality will require well designed epidemiological studies that do not suffer from the weaknesses of previous studies." *Does OEHHA disagree with any of these statements by Dr. Silverman? Specifically, does OEHHA disagree that absence of quantitative data on historical exposure precludes a causal interpretation of existing epidemiological data? If they do disagree with this statement, then what specific, objective, independently reproducible techniques does OEHHA accept for establishing a causal interpretation in the absence of quantitative data on historical exposures? Will they agree to withdraw all of their claims and interpretations about causality until they have clearly identified such techniques, applied them, and documented the results so that the public may comment on them?*

Q8.4 *How does OEHHA account for the disagreement between their (along with Bhatia et al.'s) conclusions about causality and the conclusions reached in other recently published studies, comments, and reviews (e.g., Silverman, 1998, Cox, 1997, Morgan et al., 1997, etc.)? Does OEHHA agree that these disagreements should be resolved, or at least thoroughly discussed by them in Chapter 6, and mentioned in their Executive Summary, in order to achieve a truly "comprehensive review of the literature" considering "all available scientific data" (C-OEHHA-65)?*

Q8.5 OEHHA substantially dismisses our recent analyses of causation for DE and lung cancer risk (C-OEHHA-145) on the grounds that we do not follow their approach (subtract estimated background concentrations, reconstruct exposures, exclude shopworkers, or exclude the last four years of follow-up.) However, we used nonparametric methods that do not require subtraction of estimated background concentrations and we used the exposure estimates provided to us by OEHHA. OEHHA has already agreed that including or excluding shopworkers makes little difference. Our methods are relatively robust to decisions about whether to include the last 4 years of data. Most importantly, these modeling choices do not affect the majority of our recently published comments about DE and lung cancer causation. Therefore, we ask: *How does OEHHA account for the disagreement between the findings and conclusions of Cox (1997) and OEHHA's findings and conclusions? Specifically, do they disagree with our analysis of conditional independence relations and their implications for possible causality? (If so, on what grounds do they disagree?)*

CONCERNS ABOUT FALSE POSITIVES

Our 1997 comments raised the following concerns:

Our original comment:

"OEHHA's new meta-analysis is flawed by failure to correctly calculate p-values to correct for false positives due to multiple comparisons and multiple hypothesis testing. This problem also occurs in many of the individual studies cited by OEHHA, including the studies of Garshick et al. The result is that a pattern of consistently elevated relative risks is expected, whether or not DE exposure has a positive effect on lung cancer risk. Since this is the pattern that has been observed, OEHHA's meta-analysis offers no evidence either for or against the hypothesis that DE exposure has a genuine causal association with human lung cancer risk (as opposed to merely a statistical association due to improperly controlled false positives)."

OEHHA's response (C-OEHHA-122-123):

"The theoretical underpinning of this statement is that, if multiple comparisons between exposures and outcomes are undertaken in a given epidemiological study, this increases the likelihood that there will be a positive result based on chance alone. For example, if in a given study, 10 comparisons are made (e.g., between diesel exhaust exposure and cancers of the lung, stomach, bladder, brain, kidney, and other organs), then... the probability of a positive result = 0.40 assuming that the underlying null hypothesis is true (i.e., that there is in reality no association. ...There are several problems with the commenter's suggestion. The most important is that it invokes the universal null hypothesis – i.e., that all associations observed in a given data set are random and can be attributed to chance... In the case of diesel exhaust exposure, there are several sound biological reasons to suspect that the occupational exposures to diesel exhaust would be related to lung cancer: to reject associations between these variables because the authors failed to make adjustments for multiple comparisons would be foolish."

Rejoinder:

This response illustrates OEHHA's use of "straw man" arguments to avoid responding to our stated concerns. First, they falsely state the theoretical basis of our concern about improper calculation of p-values. We do not claim that "if multiple comparisons between exposures and outcomes are undertaken in a given epidemiological study, this increases the likelihood that there will be a positive result based on chance alone." We will stipulate that it is quite possible to perform multiple comparisons between exposures and responses without raising the risk of false positives, *provided that p-values are correctly computed.*

We do not claim that multiple comparisons should not be performed, but only that when they are performed, they should be performed correctly.

Secondly, OEHHA illustrates our argument by using an example of their own devising that misrepresents our argument. In OEHHA's example, diesel exhaust exposure is compared to 10 different cancers as outcomes. Our concern involves the opposite situation: there is only one outcome of concern (lung cancer), but it is examined in multiple exposure groups, each at a 5% significance level. It is this situation that we have specifically identified as being statistically invalid and leading to incorrect p-values for studies, overly narrow confidence intervals, and a pattern of small but consistently elevated risks falsely attributed to DE exposure rather than to defective statistical methodology. Rather than making up their own example, we would prefer that OEHHA address the real examples we have already provided them. For example, here is a sample of what we have said (and sent to OEHHA) on this topic:

1. Multiple hypothesis testing and multiple comparisons bias. Many studies in Table 2 test for a positive exposure-response relation in each of several subsets of the study population, e.g., in multiple age groups, exposure groups, and/or job categories, possibly using multiple statistical models, and then report the combinations yielding statistically significant positive associations – but without reducing their p-values to compensate for the expected increase in false positives from testing multiple hypotheses on the same data. Clearly, this procedure tends to increase the expected number of false positives beyond what the reported p-values indicate.

Example 1: Garshick *et al.* (1986, p. 1242) report that, in their case-control study, "Workers 64 years of age or younger at the time of death with work in a diesel exhaust exposed job for 20 years had a significantly increased relative odds (odds ratio = 1.41, 95% CI = 1.06, 1.88) of lung cancer." This is an instance of a whole family of statements of the form "Workers who were A years or younger at the time of death and who were exposed to diesel exhaust for Y years had a significantly increased relative odds ratios for lung cancer." The probability of at least one false positive occurring among the multiple hypotheses in this family corresponding to different combinations of A (e.g., no more than 54, 59, 64, 69, 74, 79, etc. years old at death) and durations of exposure (e.g., Y = 5, 10, 15, 20, 25, etc. years) is not limited to 5% when each combination of A and Y values is tested at a p = 5% significance level. For example, if 30 different (A, Y) combinations are considered, each independently having a 5% probability of a false positive (i.e., a reported 5% significance level), then the probability of at least one false positive occurring in the study as a whole is given by the following *Bonferroni bound* (e.g., Biggs *et al.*, 1991): $p = 1 - (1 - 0.05)^{30} = 78\%$. This p-value for the whole study is more than 15 times greater than the reported significance level of 5%.

This is the type of example that truly illustrates our concerns about p-values. It remains unaddressed in OEHHA's responses.

Thirdly, OEHHA states that the "most important" problem with our argument is "that it invokes the universal null hypothesis." This is incorrect. Our concerns are not predicated on any such thing. To the contrary, we went to the trouble in our 1997 submission to provide specific references to recent, high-quality technical books and articles (which OEHHA's comments suggest they still

have not read and/or not considered) that allow for correct calculation of p-values while taking into account non-random associations among variables. For example, one of the references we provided (P. Westfall, "Multiple testing of general contrasts using logical constraints and correlations", *Journal of the American Statistical Association*, 92, 437, 299-306) begins as follows:

"Multiple testing means testing more than one hypothesis in a particular study. The well-known problem with such procedures is the inflated probability of erroneous rejections when there is no allowance for multiplicity. ...The purpose of this article is to exploit logical constraints as well as dependencies, obtaining further improvements in the power of multiple testing procedures applied to a general set of linear contrasts. The resulting method is superior to competing methods that control the FEW [familywise error rate], because it provides for specific logical constraints and for specific dependence structures, as is demonstrated via theory and examples."

Thus, there is no basis for OEHHA's response that adjusting p-values to correct for the "inflation" of apparent positive associations mentioned in this quote requires "invoking the universal null hypothesis" or making inappropriate "mechanical" corrections. This straw-man argument simply ignores the recent literature on how such corrections of p-values should be made.

Finally, the following assertion by OEHHA seems to us extraordinary: "In the case of diesel exhaust exposure, there are several sound biological reasons to suspect that the occupational exposures to diesel exhaust would be related to lung cancer: to reject associations between these variables because the authors failed to make adjustments for multiple comparisons would be foolish." Why would it be foolish? Is OEHHA trying to suggest that whenever they suspect something, they are justified in using incorrect statistics to prove it? A great many strange things (including the conclusion that DE exposure increases risk of human lung cancer) could be "proved" by such a strategy. The truth is that if a causal relation is present, then correctly analyzed facts and data, rather than OEHHA's suspicions, should suffice to establish it. So, we strongly disagree that "it would be foolish" to reject statistical associations that have not been established by correct statistical procedures, simply on the grounds that there are other reasons to suspect that such associations might be found if correct statistical procedures were used.

The question of whether hypothesized associations truly exist should be tested empirically by correct analysis of data, rather than by conformity with pre-existing beliefs. This seems essential to the scientific method. OEHHA's suggestion that biased associations and/or results of incorrect analysis should be accepted -- that it would be "foolish" not to accept them -- if they re-enforce what is already believed on other grounds, epitomizes we most strongly disagree with in their overall approach and analysis. One of our major goals is to persuade OEHHA to drop this attitude in favor of a more scientific approach that would use

heavily empirical (data-driven) methods and models and require rigorously correct analyses in order to reach conclusions.

In summary, although OEHHA is eloquent in attacking and rejecting their version of our arguments, the arguments they attack are not ours. Our concerns remain unaddressed.

Our original comment:

OEHHA (p. 6-47) notes that point estimates of relative risk tend to exceed 1 in many studies of DE exposure and cancer risk and states that "If these findings were due to chance, one would expect a more nearly equal distribution of point estimates of risk above and below unity." This is an error. It confuses findings being "due to chance" with findings being "unbiased" (equally likely to fall above or below 1). Findings due entirely to chance may nonetheless contain biases that tend to make them systematically fall above 1 rather than below it. For example, most investigators, as well as OEHHA in its meta-analysis, have engaged in "subset analysis" in which multiple subsets of workers are examined (e.g., based on age, job category, duration of exposure, etc.) and those subsets that produce statistically significant positive associations are reported. However, ***such analyses tend to systematically produce false positives (point estimates above 1) unless statistical significance levels are reduced to control for multiple comparisons / multiple hypothesis testing bias.*** Statistical techniques for appropriately reducing significance levels are available (e.g., simple, approximate Bonferroni inequality adjustments or more sophisticated and accurate Monte-Carlo methods) but do not appear to have been used by OEHHA or in the individual studies included in OEHHA's meta-analysis. Therefore, ***false positives due to chance alone (in conjunction with improper setting of p-values and confidence limits) are expected to produce a consistent tendency for relative risks to be greater than 1*** in the studies examined by OEHHA. OEHHA is mistaken in claiming that this observed pattern is evidence against a chance explanation."

OEHHA's response: Same as above.

Our rejoinder: Same as above: OEHHA has not addressed our expressed concerns.

In light of the preceding background, we now raise the following questions:

Q9.1 We claim that failure to reduce p-values for individual hypothesis tests below 5%, when performing multiple comparisons or multiple hypothesis testing, tends to produce a pattern of false positives for the study as a whole when the study as a whole also reports results at a 5% significance level or 95% confidence level. Does OEHHA agree?

Q9.2 *We further claim that an expected result of such failures to reduce p-values for individual hypotheses in studies such as those considered in OEHHA's meta-analysis is a pattern of small but consistently elevated statistical associations between DE exposure and lung cancer risk. Does OEHHA agree?*

Q9.3 *Does OEHHA agree that the studies it has cited in its meta-analysis, specifically including the studies of Garshick et al., have engaged in multiple hypothesis testing and/or multiple comparisons while failing to reduce the p-values of individual hypotheses to control for multiple comparison/multiple hypothesis testing biases? (If not, please give specific citations to where such corrections have been made.)*

Q9.4 *Does OEHHA agree that p-values for individual hypotheses must be reduced in order to correctly calculate the p-values and confidence intervals for the study as a whole, when multiple hypothesis testing is being used? (Their current response seems to deny this.)*

Q9.5 *We insist that failure to reduce p-values for individual hypotheses in multiple comparisons / multiple hypothesis testing situations is expected to lead to confidence intervals for estimated relative risks that are (a) Too narrow and (b) Rightward-shifted compared to the corrected confidence intervals that would result from reduced p-values. Does OEHHA agree? Do they agree that correctly adjusting confidence intervals by widening them and shifting them leftward could make it plausible that there is no statistical evidence of an association between DE exposure and lung cancer, other than that due to chance?*

Q9.6 *OEHHA states (p. 6-56) that "If these findings were due to chance, one would expect a more nearly equal distribution of point estimates of risk above and below unity." Do they agree that failure to reduce p-values for individual hypotheses in multiple comparisons / multiple hypothesis testing situations also tends to produce "a consistent tendency for point estimates of relative risk to be greater than unity"?*

Q9.7 *OEHHA (p. 6-58) concludes that "The many associations found between lung cancer and diesel exposure are unlikely to be due to chance." We believe that we have identified a mechanism by which chance can account for precisely the observed pattern of many small associations, namely, false positives produced because of incorrect p-values for the many studies that performed multiple hypothesis testing. In light of this discussion, will OEHHA withdraw its assertion that the observed associations between lung cancer and diesel exposure are "unlikely to be due to chance"? (If not, then what is the technical basis for their conclusion? What numerical probability or probability bound does OEHHA calculate for the likelihood that the observed associations are due to*

chance? What objective, independently reproducible, statistical tests does OEHHA use as a basis for rejecting chance as the most plausible explanation for the observed associations between lung cancer and diesel exhaust?) We believe that such tests must be clearly identified, carried out, results reported, and the public given a chance to comment on them before OEHHA's conclusion can be accepted as sound. We have previously provided OEHHA with references to appropriate tests to use in cases involving multiple comparisons / multiple hypothesis testing. They have elected not to use any of them. We therefore conclude that the likelihood that the observed associations are due to chance has not been tested by OEHHA, and that it is logically invalid and misleading for them to reject chance as a likely explanation.

Q9.8 OEHHA states that "There are several sound biological reasons to suspect that the occupational exposures to diesel exhaust would be related to lung cancer: to reject associations between these variables because the authors failed to make adjustments for multiple comparisons would be foolish." We challenge the premise of this assertion in other comments. Here, we ask: *What is OEHHA's basis for claiming that "it would be foolish" to reject associations between these variables because the authors failed to make adjustments for multiple comparisons? We believe that it is not only not foolish, but indeed an essential part of the statistical experimental method to reject (or, more accurately, to suspend judgment and "not accept", in statistical parlance) hypothesized associations in the absence of data and correct data analyses to support them. The logic behind this approach is that, if the alleged associations are real, then correct data and analysis will reveal them; hence, there is no need to assume them in the absence of empirical tests that support them.*

4. CONCERNS ABOUT OTHER BIASES

Our 1997 comments included the following arguments and concerns.

Our original comment:

"As a second example of how findings due to chance alone can systematically tend to produce relative risks greater than 1, suppose that exposure has no effect on cancer risk but that there is some heterogeneity in individual cancer risks. For example, suppose that the probability of death with lung tumor is 0.2 among sensitive people and 0.1 otherwise, and that half the population is sensitive (independent of DE exposure). Randomly matching exposed individuals with similar unexposed controls and computing relative risk would give four possible relative risk ratios: $0.2/0.2 = 1$, $0.1/0.2 = 0.5$, $0.2/0.1 = 2$, and $0.1/0.1 = 1$. These four outcomes are equally likely, since the distribution of risks is identical in the exposed and unexposed populations. Hence, the average relative risk obtained from a large number of such matchings will be $(1 + 0.5 + 2 + 1)(1/4) = 4.5/4 = 1.125$. In other words, the point estimate of the relative risk

exceeds 1 even though exposure has no effect on risk. This simple example illustrates a principle that holds more generally: relative risk calculations that ignore heterogeneity in individual response probabilities within groups may be biased upward. Both OEHHA's proposed models and the risk models used in key studies relied on by OEHHA (such as those of Garshick *et al.*) make this mistake."

OEHHA's response (C-OEHHA-149): "The commenter proposes a hypothetical situation in which genetic susceptibilities for lung cancer are equally distributed between exposed and unexposed groups... However, the commenter puts forth no empirical evidence supporting his assumptions. Moreover, despite his superficially appealing example, it is well accepted in epidemiological theory that a potential confounder (e.g., genetic susceptibility) that is independent of exposure does not meet the definition of a confounder and will not influence the estimate... It is unlikely that only positive confounding would occur..."

Rejoinder:

This is a great example of a straw-man argument by OEHHA. Our original comment assumes nothing about genetic susceptibilities and makes absolutely no hypotheses about how genetic susceptibilities are distributed in different groups. Our point is a purely arithmetic one: risks expressed as ratios are biased upward when people in the same group have different risks. OEHHA's criticism that "the commenter puts forth no empirical evidence to support his hypothesis" is inappropriate, as arithmetic demonstrations do not usually require empirical evidence. The claim that "It is well accepted in epidemiological theory that a potential confounder (e.g., genetic susceptibility) that is independent of exposure does not meet the definition of a confounder and will not influence the estimate" seems irrelevant. The claim that "It is unlikely that only positive confounding would occur", although irrelevant, suggests that OEHHA misunderstands the point of the example. The reason that the expected value of the ratio is greater than 1 is *not* that there is a mysterious bias due to some unknown distributions of genetic susceptibilities in the exposed and unexposed groups. (Recall that, by hypothesis, the groups are identical in all ways that affect risk.) The reason is simply that ratios are inherently asymmetric: big numbers in the denominator cannot reduce the ratio below 0, while small numbers in the denominator can make the ratio arbitrarily large. So, averaging over the various possibilities leads to averages that slightly but systematically exceed 1. As we originally stated, this simple example illustrates a general principle: the ratios are always biased up, not down, because ratios can exceed 1 by large amounts but can be less than 1 by no more than 1.

In our 1997 submission, we recommended specific appropriate methods for dealing with heterogeneities and biases of the type illustrated in this example (see e.g. Table 4 of our 1997 submission, C-OEHHA-140). As we feared and

predicted (C-OEHHA-143), OEHHA has elected to neither respond to nor follow these recommendations (or any of our other tabulated recommendations).

We have only three questions about this example

:
Q10.1 Does OEHHA agree with our arithmetic in the above example?

Q10.2 Does OEHHA agree that this arithmetic shows how relative risks systematically greater than 1 can be produced in the absence of any cause-and-effect impact of exposure, i.e., "due to chance alone", as we originally claimed?

Q10.3 Does OEHHA agree that it is possible for risk ratios to display a pattern of small but consistent elevations even when the true excess risk due to exposure is zero?

Our original comment:

OEHHA states (p. 6-47) that "In the studies with the more complete diesel-related exposure and duration of employment information, several identified exposure-response relationships, including the two studies by Garshick et al." But no such exposure-response relationships have been unambiguously identified. For example, in their cohort study, Garshick *et al.* (1988, p. 823) conclude that "In this study we demonstrate an association between diesel exhaust exposure and lung cancer." However, as described by the authors, "With recent exposure included, no evidence of a consistent exposure duration-response relationship was obtained... When exposure in the year of death and the 4 years before were disregarded... the group with at least 15 years of exposure (with current exposure not included) had a relative risk of lung cancer of 1.72 (95% CI = 1.27, 2.33)", emphasis added.) For the authors to exclude the most recent four years worth of data is an *ad hoc* truncation of the data that generates a positive result in this study but not in the case-control study, where "the relative odds ratio of lung cancer decreased slightly with recent exposure disregarded" (*ibid.*, p. 823). A positive result created only by selectively discarding data (or, equivalently, selecting a subset of the data to analyze), with the selection being made differently in different studies to maximize positive results, clearly runs the risk of being a false positive. For OEHHA to assert that such ambiguous evidence "identified an exposure-response relationship" is misleading.

OEHHA's response: None.

Q11 Does OEHHA agree that unambiguous exposure-response relations have not yet been identified in any studies, specifically including the studies of Garshick et al.? (If not, please identify which specific studies OEHHA believes identify unambiguous exposure-response relations. The motivation for this

request is that we believe that every study reviewed by OEHHA contains problems, similar to those in the Garshick et al. studies, that invalidate interpreting their results as evidence of exposure-response relations.)

Q12.1 OEHHA states (p. 6-56) that several studies "found significant elevated risks associated with the subgroup having the longest duration of employment." They also state (p. 6-57) that "The meta-analysis identified evidence of exposure-response relationships in the subgroup analyses based on duration of employment." *Does OEHHA recognize that partitioning a population into different subgroups based on criteria such as duration of employment is a form of multiple hypothesis testing? Do they recognize that this process creates multiple hypothesis testing bias in findings of significant association, unless p-values are adjusted downward? (See Biggs et al., 1991, for details of the biases created by such partitioning. We have previously supplied this reference to OEHHA and strongly urged them to use it before drawing conclusions from their "subset analysis". They appeared to have ignored this along with all of our other tabulated recommendations, see e.g., C-OEHHA-138 to 140.) Does OEHHA agree that both they, in their new "subgroup" analyses, and the other investigators they cite to support the finding of elevated risks in longest-duration subgroups, have not made the p-value adjustments recommended by Biggs et al. (1991) and the other references we have cited on this point?*

Q12.2 OEHHA states (p. 6-56) that several studies "found significant elevated risks associated with the subgroup having the longest duration of employment." However, by using cumulative exposure as an exposure metric, they have confounded duration of employment with both expected cumulative exposure to DE and with exposure to any other carcinogens in the workplace. *Does OEHHA agree that, when cumulative exposure is used as the dose metric, then if there are any carcinogens in the workplace that cause lung cancer (not necessarily diesel exhaust), the longest-duration employment groups may tend to have elevated lung cancer risks, even if DE exposure itself has no effect on lung cancer risk? To avoid this potential confounding, we have previously recommended that OEHHA clearly separate the roles of DE exposure concentration and exposure durations in their models and analyses. OEHHA neither responded to nor followed this recommendation, as with all the rest of our tabulated recommendations on modeling and methodology (C-OEHHA 138-140). When we implemented this suggestion in our own reanalysis of the Garshick et al. data (Cox, 1997), we discovered that estimated DE exposure concentration is uncorrelated with lung cancer risk, but that duration of employment in DE-exposed (and presumably other chemical-exposed) work places is associated with lung cancer risk. We interpret this as strong evidence against the hypothesis that DE is the relevant causal agent. We again urge OEHHA to conduct a similar analysis for itself, in which the roles of DE exposure concentration and duration of employment are clearly separated.*

Our original comment: "It is also misleading to characterize the two studies of Garshick *et al.* as having 'more complete diesel-related exposure information', since no exposure information whatsoever was available for the individuals in these studies.

OEHHA's response (p. C-OEHHA-150): "OEHHA staff agree with the commenter that the characterization of this information in the prior draft could be somewhat misleading and have modified the text in the revised version."

Rejoinder: We thank OEHHA for responding to one of our comments.

Our original comment: "The apparent exposure-response relationship may be due partly to ignored exposure measurement error (Carroll, 1997). OEHHA has deliberately refused to use appropriate measurement-error models. See page C-OEHHA-168 [of the 1997 draft]. Here, a discussion of measurement errors in simple linear regression models of doubtful relevance to binary outcomes (lung cancer or no lung cancer) is followed by the statement that 'OEHHA staff, then, do not agree that the realism of the present approach needs to be improved' by allowing for exposure measurement errors. ... OEHHA's risk model ignores exposure measurement errors and uncertainties that can lead to inflated risk estimate. In threshold models, the bias is upward and can be large (Carroll, 1997). OEHHA should use a model with exposure uncertainties, since exposures are unknown." (Table 3, C-OEHHA-138)

OEHHA's response: None

Q13 OEHHA still uses a model that does not account for measurement error. They still maintain (p. 6-55) that "Hence, while exposure misclassification clearly occurs in studies such as these, the result of random misclassification is to underestimate, rather than spuriously elevate, risk estimates."

Q13.1 *Did OEHHA read the paper we referred them to on this point?* (R.J. Carroll, "Surprising effects of measurement error on an aggregate data estimator". *Biometrika*, **84**, 1, 231-134.) Did they find any error in it? Similarly, do they agree with K.J. Rothman and S. Greenland, *Modern Epidemiology* 2nd Ed., Chapter 8, that "Contrary to popular misconceptions, however, nondifferential exposure... can sometimes produce bias away from the null", specifically when exposure has more than 2 levels (as in the Garshick studies?)

Q13.2 *In light of the above reference, does OEHHA agree that the effect of random misclassifications in models with dichotomous outcome variables (such as lung cancer risk models) is not as they have described it?*

Q13.3 Does OEHHA now concede that misclassification error is likely to overestimate, rather than underestimate, risks in such models?

Q13.4 Will OEHHA agree to withdraw their claim that the pattern of elevated risk estimates in DE-exposed populations is unlikely to be due to exposure estimation error, at least until they have applied appropriate statistical models that include exposure classification errors?

Q14. OEHHA concludes (p. 6-58) that "Also, with the possible exception of the studies that did not take smoking into account, the findings reviewed above are unlikely to be due to confounding or bias." This claim appears to be based on considering only a few of the many plausible potential sources of confounding and bias. For example, OEHHA addresses only smoking, asbestos, and diet as potential confounders (6-53 to 6-55). But birth year, death year, duration of employment, and age at retirement are all potentially confounded with DE exposure in OEHHA's analysis. (Although they have attempted to avoid this logical problem using "subset analysis" to stratify the worker population, they have failed to correct for the multiple hypothesis bias that this procedure introduces.) Similarly, OEHHA briefly addresses recall and selection bias (6-55), but neglects to address other potential biases such as history, instrumentation, regression, differential mortality, and interactions (Campbell and Stanley, 1963), or model selection bias and extrapolation and attribution bias, all of which we have previously identified to OEHHA as potential biases that must be controlled for (see Table 5 of our 1997 submission, C-OEHHA-141).

Q14.1 Does OEHHA agree that its discussion of potential confounding variables has omitted confounding of DE with other workplace chemicals?

Q14.2 Does OEHHA agree that DE exposure is potentially confounded, in various studies that it cites, with one or more of the following: birth year, death year, duration of employment, and age at retirement? Do they agree that none of these variables has been discussed in their section on potential confounders?

Q14.3 Does OEHHA agree that its discussion of potential biases omits multiple hypothesis testing bias, history bias, and model selection bias, among others?

Q14.4 Does OEHHA agree that multiple hypothesis testing bias, history bias, and model selection bias are all relevant to the studies they have reviewed, specifically including those of Garshick et al. (as detailed in Cox, 1997)?

Q14.5 In light of these considerations, does OEHHA agree that its claim that "...the findings reviewed above are unlikely to be due to confounding or bias" has not yet been established? (In particular, we consider multiple hypothesis testing bias and model selection bias to be very likely explanations for the observed pattern of associations between DE exposure and lung cancer risk in

past epidemiological studies. Until all the plausible sources of confounding and bias have been considered, it is not valid to infer or state that they are "unlikely" to explain the observed associations.)

Q14.6 Is OEHHA willing to withdraw its assertion that "...the findings reviewed above are unlikely to be due to confounding or bias" until it has considered the sources of confounding and bias that we have identified and that they have not previously addressed? (If not, what objective basis does OEHHA offer for its conclusion, given that it has not yet addressed history bias, multiple hypothesis testing bias, and so forth?)

5. CONCERNS ABOUT MODELS AND METHODS

New summary comment: OEHHA continues to assume linear, no-threshold dose-response models for both human and animal data, even though available evidence provides stronger support for nonlinear and threshold-like models. It still refuses to test this assumption or to use methods that do not require it. This injects a major source of uncertainty into all of OEHHA's conclusions about risk. But, they omit this major uncertainty from their calculations, thus obtaining confidence bands and confidence limits for risk that ignore substantial model uncertainty. We believe that, once this uncertainty is included in the analysis, the confidence intervals will all include 1 (zero excess risk due to DE exposure) as a very likely value.

More generally, OEHHA has neither responded to our tabulated concerns nor followed any of our tabulated recommendations on modeling and methodology (Tables 3-6, C-OEHHA-138 to 141). We will not repeat these here, but request that OEHHA respond to them by stating (a) Whether they agree with each of our stated concerns; (b) Agree that our recommendations are appropriate; and (c) Agree to revise their analysis to take into account those recommendations that they consider appropriate to address concerns that they agree are valid. We will be willing to provide detailed references, software, and/or assistance to OEHHA in responding to our previously tabulated concerns.

Our original comment: "In summary, we recommend that OEHHA not enforce a straight-line fit to the nonlinear data. This methodological choice drives the rest of their risk analysis. It is based purely on an *ad hoc* assumption rather than on data or sound, clearly applicable theory. A better, equally practical alternative would be *model-averaging* (Buckland *et al.*, 1997), in which the true form of the relationship between exposure and response is treated (realistically) as unknown, and the data are used to weight different possible options, including linear and nonlinear possibilities.

Finally, how much numerical difference would a more flexible modeling approach be expected to make in OEHHA's quantitative risk estimates based on the Garshick data? As a very rough approximate bound, suppose that there are k alternative models that are considered at least as plausible as OEHHA's linear model. If these alternative models specify zero increased risk at low doses, then OEHHA's risk estimate should be reduced by at least $1/k$ (and further if the alternatives are more plausible than the linear model). In our opinion, a value of at least $k = 4$ is realistic, since there are at least three alternative models (quadratic, cubic, and threshold) that are at least as plausible as OEHHA's linear model. Thus, we would expect that accounting for model uncertainty in the Garshick data reanalysis via model-averaging would reduce OEHHA's risk estimates (MLE and UCL) by at least a factor of 4."

OEHHA's response (C-OEHHA-146): "The idea of averaging over models to get a slope at the origin is an interesting one, apparently not tried, per se, in risk assessment. A common approach seems somewhat similar, taking the geometric mean of all candidate values for unit risk. The current work simply gives the range of all the candidate values for upper confidence limits on unit risk, based on analyses that assume an essentially linear relation..."

Rejoinder: We consider this an example of a non-responsive response. We recommended Bayesian model averaging because we believe that it would give a more realistic assessment of uncertainties. We already knew that it has not been tried – that is the point. The model-averaging approach is entirely different from assuming an answer to the main uncertainty (is the dose-response relationship linear?) and then taking a geometric mean (or other aggregation) of values that presuppose the answer. Bayesian model averaging (and also use of model-free methods, which we have repeatedly advocated without apparent effect on OEHHA) are directed at discovering the true relationship, rather than assuming it. They are able to give realistic assessments of uncertainty, rather than assuming away the most important uncertainties (namely, model uncertainties).

Our original comment: (The original comment was made for rat data, but applies equally well to modeling of epidemiological data). "OEHHA could reduce the expected error introduced by its preselection of... mathematical model forms by considering a wider range of risk models that allow for the possibility that the dose-response function is zero or sub-linear at sufficiently low doses. Practical ways to do this include the following:

- (a) *Model-averaging and model-weighting techniques* (Buckland *et al.*, 1997; Berger and Pericci, 1996). This approach deals with model uncertainty by allowing for a wide set of possible theoretical models and using the experimental data to judge their relative plausibility. Buckland *et al.* (1997) describe simple versions for use in applied work, directly addressing

OEHHA's expressed concerns about the complexity involved in doing a better job.

- (b) *Model-free estimation methods* e.g., nonparametric regression models (Hall and Turlach, 1997), model-free curve fitting, and computationally intensive smoothing methods that only require weak assumptions, e.g., that the dose-response curve be smooth, or that it be monotonic, or s-shaped, etc. These methods deal with uncertainty about the correct model by making very few assumptions and solving for the dose-response curve that best describes the empirical data points, without imposing any very strong theoretical preconceptions.
- (c) *Computationally intensive model selection methods* (e.g., Shao, 1996). This strategy searches for the dose-response model that minimizes estimated prediction errors, based on the available data.

However, OEHHA has chosen to consider only the Weibull multistage and simplified Moolgavkar models. In defending this choice, OEHHA states (p. 7-10) that "The analysis works with models that are considered to be the most plausible, and is not concerned with a mathematically complete set of alternatives that have no previous justification... However, the mathematical alternatives are difficult to rule out and may be considered to be a source of uncertainty." This reflects a misunderstanding of the nature of modern techniques such as model-free curve-fitting and nonparametric regression. The goal of these techniques is not to introduce unjustified alternatives to be ruled out, but rather to avoid introducing unnecessary theoretical assumptions in fitting dose-response curves to experimental data. As much as possible, the data should be allowed to determine the model that is used to describe the dose-response relation. It should select from a large set of *a priori* possibilities, with enough flexibility to adequately reflect the data (something that the Weibull multistage model has been criticized for not doing). Rather than either selecting or rejecting mathematical models that imply low-dose linearity *a priori*, for example, modern techniques attempt to let the experimental data determine the weight to be given to linear vs. nonlinear possibilities.

OEHHA does not know how (or whether) DE could cause cancer at low doses, so claiming that it has selected models that "are considered to be most plausible" (p. 7-10) is unwarranted. Many scientists, including Mauderly, have suggested that threshold or low-dose nonlinear models are more plausible than the ones that OEHHA has selected. When the most plausible models are not known, model-free techniques seem appropriate and should be used in addition to, or in preference to, pre-defined parametric models.

OEHHA's response (C-OEHHA-133), paraphrased: When OEHHA looks at several other models that all assume no threshold and linearity, they get results

that are similar. Therefore, and given that the rat data won't be used in their final risk estimates, they don't want to consider methods that would allow these assumptions to be tested or overridden by the empirical evidence in the data.

Rejoinder: It is obvious that if OEHHA only considers models that make the same key assumptions, they will get similar results. The purpose of using the methods we have recommended is to see whether the assumptions are justified. We understand that OEHHA is unwilling to do this for rat models, but urge that they not present even "informational" risk assessment based on rat data unless they consider models that allow for low-dose nonlinearity. We have previously commented, and OEHHA seems to accept, that low-dose nonlinear models fit the data better with fewer parameters, and give much lower risk estimates.

Setting the rat data aside, we urge OEHHA to apply the above methods to any epidemiological data that they use for risk assessment purposes. Otherwise, we believe that their uncertainty characterizations (including confidence bands for odds ratios and confidence limits for risk estimates) will be flawed by improperly ignoring model uncertainties.

Q15.1 Does OEHHA agree that model-averaging and model-free techniques such as those we have advocated are appropriate for data analysis when the correct model is highly uncertain?

Q15.2 Does OEHHA agree that, were these methods to be used, they would tend to lead to wider confidence intervals for estimated relative risks (because they would be more sensitive to model uncertainties?)

Q15.3 Does OEHHA agree that it is plausible that, were they to use the methods we have advocated, they would discover that the 95% confidence intervals for estimated risks from DE exposures include zero? (We have already offered a rough, conservative calculation suggesting that there is at least a 75% probability that the low-dose risk is zero or essentially zero, provided that methods are used that express uncertainty about models.)

Our original comment: OEHHA suggests that the Garshick *et al.* data support a linear model over a threshold model and that '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 evidence of real sublinearity' (C-OEHHA-170). These suggestions are flatly contradicted by the data. Formal statistical tests confirm what is visually apparent in Figure 7-3: that a threshold model fits the data significantly better than a linear model. OEHHA responds that 'consistent with the theoretical constraint', a linearized multistage model would (by definition) include a positive low-dose linear component (*ibid.*). But there is no theoretical constraint in the multistage model that requires a positive linear term. The linearity that OEHHA refers to as a "theoretical

constraint" is imposed as a regulator's convention (unjustified by statistical theory) in constructing confidence bands. In truth, if a nonlinear (e.g., purely quadratic or cubic) model were known to be correct, then correctly computed upper confidence limits would not be linear, but would approach zero at the origin."

OEHHA's response (C-OEHHA-146): The old Figure 7-3 has been removed and replaced by results of a very different new analysis.

Rejoinder: We have not had time to understand and review OEHHA's new analysis, which differs radically in its approach from previous drafts. However, the new Figure 7-3 appears to confound duration of exposure to the workplace with magnitude of exposure to DE. It also appears to have neglected to correctly control for multiple hypothesis testing bias arising from its use of multiple duration groups. Most importantly, it, too, seems to leave unaddressed the crucial question of whether the data are more consistent with a threshold or non-linear (essentially zero excess risk at low doses) model than with a linear non-threshold model.

Our original comment: ..."Many of the identified areas of uncertainty could be resolved relatively easily using more appropriate statistical methods. ... Technically, models that represent uncertainty in exposure estimates, allow for interindividual heterogeneity, and are flexible enough to admit the possibility of low-dose nonlinearity would appear to be unambiguously more appropriate for modeling DE risk data than models that don't. However, OEHHA has chosen not to use such methods, instead opining that the techniques they have used, despite their recognized errors and limitations, produce answers that might not be very inaccurate and that OEHHA considers "adequate" (C-OEHHA, 167, 168, 170). OEHHA's criteria for model adequacy are not stated. The basis for preferring simpler, less correct models to more complex, more accurate models is unclear, given the capabilities of modern statistics software."

OEHHA's Response: None

Q16.1 *What formal criteria or tests does OEHHA accept for determining model adequacy and/or for deciding which risk models should be considered as candidates for estimating risk?*

Q16.2 *Have these criteria been applied to OEHHA's own choice of risk models and to a variety of competing models? If so, what models were considered and what were the results?*

Q16.3 *Does OEHHA agree that a fully adequate characterization of risks and uncertainties for DE requires considering a range of models and modeling assumptions, including models that allow for the possibility of zero risk at low*

doses (or at all doses)? If not, how does OEHHA propose to incorporate model uncertainty into its risk characterization and confidence limits – an essential step (Buckland et al., 1997) that it has not yet taken?

6. CONCERNS ABOUT BIOLOGICAL PLAUSIBILITY AND MISREPRESENTATION OF SCIENTIFIC KNOWLEDGE

New Comment:

OEHHA's new Section 6.1.6 suggests that there are several alternative hypotheses about the causal mechanisms of DE-induced carcinogenesis, putting them all on a roughly equal footing. We are concerned that this is misleading, in that (a) It fails to acknowledge the overwhelming experimental evidence for the role of threshold (lung over-burdening) mechanisms in all experiments where excess tumors have been observed; and (b) It fails to acknowledge or discuss the increasingly large literature that casts doubt on the biological plausibility of the other (low-dose, non-threshold) suggested mechanisms. We consider that the present discussion does not fairly represent current thinking or literature on the likely causal mechanisms of DE carcinogenicity. We are willing to provide the required literature overview ourselves if OEHHA is not. Our major concern here is that OEHHA uses a negative (it is not possible to prove the absence of a low-dose mechanism) and *in vitro* biological evidence that many investigators consider ambiguous at best, to justify its claims that a causal relationship between DE and human lung cancer is "reasonable and very likely" (6-59). We believe that this is unjustifiable and presents a misleading impression to policy makers and decision makers about the probable consequences of reducing public exposures to DE. Specifically, we believe that the most likely impact of reduced DE exposure will be no change in lung cancer risk, since we have seen no evidence that would make it plausible that there is a causal relationship between them at relevant exposure levels.

Q17.1 *On what grounds does OEHHA claim (p. 6-59) that "The temporal relationship between exposures and lung cancer is consistent with a causal relationship?" Does OEHHA have any evidence that DE exposure prior to lung cancer initiation is a better statistical predictor of lung cancer risk than DE exposure following lung cancer initiation? Or do they simply mean that most people develop lung cancer in old age, after they retire? (If the latter is what they mean, then would not OEHHA admit that this temporal relationship is irrelevant to determining whether there is a causal relationship?)*

Q17.2 *What specific, objective, independently reproducible criteria does OEHHA use to conclude that it is "very likely" (6-59) that DE exposure causes the increased risks of lung cancer observed in epidemiological studies? What numerical probability or range of probabilities, if any, does OEHHA assign to this*

allegedly "very likely" event? (We do not agree that this is "very likely" or even "plausible". Instead, we propose that it is far more consistent with the evidence to believe that false positives from multiple hypothesis testing, and other non-causal explanations that we have discussed, explain the observed increases in estimated risks. We have already suggested why we put an upper bound of 1/4 on the probability that OEHHA's claim is correct.)

Q17.3 *How does OEHHA reconcile this conclusion with the opposite conclusions reached by other, truly independent reviewers? (We exclude Bhatia et al. from this category.)*

Q17.4 *If the correct dose-response relationship model were known to be purely cubic or quadratic, then would OEHHA agree that the 95% UCL on risk (computed by correct statistical procedures rather than regulatory conventions) must approach zero at sufficiently low doses?*

Q17.5 *How does OEHHA believe that the possibility of zero excess risk at low doses should be incorporated into its range of risk estimates? Does OEHHA agree that their currently presented range of UCLs for risk estimates ignores the possibility of zero risk at low doses? Do they agree that other models (e.g., purely cubic or purely quadratic models) that have essentially zero risk at sufficiently low doses (zero slopes at the origin) are also not represented in their current range of risk estimates?*

Q17.6 *Does OEHHA agree that a fully adequate characterization of risk and uncertainty for DE and lung cancer must include the possibility (in our judgment, the strong probability) of zero or nearly zero excess risks at low doses? (If not, how does OEHHA justify excluding these possibilities from their uncertainty analysis?)*

Q17.7 OEHHA states (ES-25) that "OEHHA recognizes that the limited exposure information available does contribute to the overall uncertainty of the dose-response risk assessment... However, the overall magnitude of the associated uncertainty is not unduly large. ... OEHHA provides a tabular range of risk so as to fairly capture the scope of the uncertainty in these analyses." We disagree that OEHHA's ranges fairly represents the range of uncertainty in these analyses. Specifically, we note that other apparently reasonable estimates of exposure, such as the estimates previously used by Dr. Crump, lead to a conclusion of no significant excess risk of lung cancer due to DE exposure. Although OEHHA considers its own estimates more plausible than Dr. Crump's, we believe that they should recognize that there is some probability that *knowledge of the true exposure pattern could produce a finding of zero excess risk associated with exposure*. In other words, we do not consider it reasonable to reject this possibility based on the little that is known about exposure. Indeed, OEHHA characterizes the changes in its own assumptions about exposure

patterns in the Garshick *et al.* study from draft to draft as reflecting "thinking afresh the likely peak exposure of workers on trains in 1959" (C-OEHHA-83). This indicates to us that there is considerable room for further changes in assumptions about exposure patterns. We therefore ask:

Q17.7.1 *Does OEHHA agree that some other investigators might reasonably assume, taking into account the limited exposure information available, patterns of exposure that do not lead to a finding of statistically significant excess lung cancer risks due to DE exposure?*

Q17.7.2 *Does OEHHA agree that risk estimates based on exposure patterns that might reasonably be assumed by other investigators should be included in their ranges of risk, in order to fairly capture the scope of the uncertainty in their analysis (viewed as one among several equally or nearly equally plausible analyses that might reasonably be carried out)?*

7. CONCERNS ABOUT PROCESS

In our 1997 submission, we made the following recommendations (Table 3 of our 1997 submission):

- Let the data influence the weight given to different (e.g., linear vs. nonlinear) modeling possibilities (Lee 97, Gonzelez-Manteiga 96)
- OEHHA should use a model with exposure uncertainties, since exposures are unknown.
- Use appropriate statistical models (e.g., Ahn & Chen, 1997, Becker, 1997) that allow for interindividual heterogeneity.
- Treat exposure concentration and exposure duration as two separate factors in risk modeling. Let the data determine whether only their product affects risk; don't assume it.
- Pick the most appropriate model for the data via goodness-of-fit or other formal criteria (see Table 4), and/or use nonparametric regression.
- Apply relevant tests for causality (Table 6). The individual studies cited in the meta-analysis do not establish a causal relation between DE and lung cancer and do not test the hypothesis of alternative causes such as multiple comparisons bias.

- Correct for multiple hypothesis testing bias by using appropriate p-value adjustments (Efron, 1996; Toman, 1996; Westfall, 1997).

OEHHA has neither substantively addressed nor followed any of these recommendations. We are concerned that they continue to promulgate policy-relevant documents based on informal, subjective judgments and criteria while neither disagreeing with nor accepting our recommendations that they use what we consider to be more neutral, accurate, and appropriate methods.

We are especially frustrated because we believe that a technically correct, neutral (i.e., unbiased) data analysis would lead to the conclusion that there is no evidence that DE exposure causes increased human lung cancer risk at relevant exposure levels. We see OEHHA as providing data interpretations and analyses that will tend to give policy makers reason to regulate DE exposure more tightly, where a better understanding of the data, the analyses, and their limitations would encourage no such action. Yet, OEHHA has the power to simply ignore our concerns and recommendations. If they succeed in doing so and the result is a bad policy, expensive to implement and producing zero cancer risk reduction health benefits, it is not OEHHA who will have to bear the costs. Therefore, we urgently solicit OEHHA's help in resolving the many unaddressed concerns we have raised.

Q18.1 Does OEHHA agree that there is substantial probability that reducing DE exposures further would create no significant additional reductions in lung cancer risk, either because of lack of a true causal relation between them at low doses or because the unknown dose-response relationship approaches a zero slope at the origin?

Q18.2 Can OEHHA give decision-makers a useful lower-bound estimate of the probability that reducing DE exposures would prevent no additional cancer deaths? (We believe that 75% is a very conservative lower bound, based on the rough reasoning previously outlined. 90% might be a more realistic estimate.)

Q18.3 Does OEHHA agree that the concerns we have raised about their analysis apply equally well to previous analyses and interpretations of causality for DE offered by other authoritative bodies?

8. SPECIFIC TECHNICAL CONCERNS ABOUT OEHHA'S NEW ANALYSIS

New comment:

Pages 7-18 to 7-26 and the new Appendix D contain the heart of OEHHA's new risk assessment. This new assessment departs radically from

previous drafts in crucial respects, including the risk models considered, the attempt to quantify individual-level hazard functions, the statistical methods used, the ways in which data are used, and the assumptions introduced. In effect, it is a new risk assessment, although its conclusions are little changed from those in previous drafts.

We have grave technical concerns about this new risk assessment. The major categories of concerns are as follows:

- This is a new risk assessment, not a refinement of previous ones. OEHHA has produced a substantially different risk assessment with a new methodology, new models, and (in our judgment, as discussed next) new errors that compromise its technical validity. Thus, the total time that the public has had, as of this submission, to evaluate the risk assessment that OEHHA is now proposing to use is only a few weeks – the time since its release of the new assessment. This is a departure from the usual process of providing the public with adequate opportunity to review and comment on proposed risk assessments. We do not feel that we or others have been given adequate opportunity to address the radically revised approach that OEHHA has taken since the last draft.
- Questionable assumptions and methods. The assumptions that OEHHA has used for its quantitative risk assessment come largely from a single paper that many, including its lead author, consider inappropriate for quantitative risk assessment. As stated by OEHHA (p. 7-26), "The assumptions not otherwise specified here are essentially those of Garshick *et al.* (1988)." We and many others maintain that these assumptions are not appropriate for purposes of quantitative risk assessment. They contain many approximations (e.g., the "rather irregular boundary points on years of exposure" noted by OEHHA, p. 7-26) that affect the quantitative results and that are subject to criticism on a variety of technical grounds. Had OEHHA previously announced that it was going to base its risk assessment to such a large extent on this single paper, then we would have provided comments on the major technical flaws and limitations in that paper and some possible ways to remedy them. (See e.g., P.J. Green, "Reversible jump Markov chain Monte Carlo computation an Bayesian model determination", *Biometrika*, **82**, 4, 711-32, 1995 for a modern approach to estimating step functions such as those posited in the Garshick *et al.* paper.) As it is, we note here that we disagree with many of the assumptions and methods of the Garshick *et al.* paper in light of subsequent work by Garshick and others. We do not believe that the paper provides an appropriate basis for quantitative risk assessment, and we believe that the risk estimates that OEHHA has derived based on it do not adequately reflect the many uncertainties in the assumptions made.

- **Non-standard approach.** The methodology that OEHHA has adopted does not use standard or generally accepted methods of regulatory risk analysis. It consists of an incoherent mix of methods and models (e.g., combining parameter values estimated from a conditional logistic regression model with linear relative risk and other assumptions that are inconsistent with the logistic regression form). It makes apparently *ad hoc* assumptions and decisions about the model formulas to be considered, makes critical substantive assumptions such as low-dose linearity without providing empirical or theoretical justification for them specifically for DE, and uses uncertainty analysis methods and numerical confidence interval calculations that do not correctly account for all the relevant uncertainties. In places, it appeals to formulas (e.g., Armitage-Doll cancer risk models) that have not been shown to be applicable to DE, and it uses mathematical approximations that are known to over-estimate risk in many situations. The overall approach (fitting a straight line to estimated duration-response points) lacks endorsement from any wider risk analysis or regulatory community.

Although the lack of time given for a thorough review and careful discussion precludes full analysis of these general concerns, the following initial set of questions illustrates the breadth and depth of the technical issues that remain to be resolved. These issues need to be addressed before the approach that OEHHA is now taking can be judged technically sound and useful, or capable of supporting credible quantitative risk estimates.

Q19 OEHHA states (p. 7-23) that "Relative risks are fitted linearly to duration of exposure."

Q19.1 Does OEHHA agree that the intercept for any such linear fit should go through the origin (i.e., zero duration of exposure creates no additional risk?) Do they agree that their straight-line model in Figure 7-3 does not go through the origin? If so, how (if at all) do they propose to revise their risk model? Do they agree that their final risk model should assure that DE to which people are not exposed is not assigned a positive excess risk of lung cancer?

Q19.2 Does OEHHA recognize that the linear relative risk model they have used could, logically, imply lung cancer probabilities larger than 1 for people with sufficiently large durations of exposure? Does OEHHA intend to revise their calculations to use a more standard risk model that cannot in principle predict probabilities greater than 1? If so, what criteria will they use to select one or more risk models for consideration?

Q19.3 Does OEHHA agree that their assumption that relative risk increases linearly (or log-linearly) with exposure duration is mathematically inconsistent with the assumptions of the proportional hazards and logistic regression models

used by Garshick? Do they recognize that this mathematical inconsistency is potentially numerically significant for risks (such as lung cancer risk) that are not rare?

Q19.4 *What biological justification, if any, does OEHHA have for assuming that relative risks (as opposed to absolute risks, for example) increase linearly (or log-linearly) with exposure duration? We challenge the plausibility of this assumption and request a detailed explanation of why it was made, what competing alternatives were (or should have been) considered, what criteria were used to reject the alternative assumptions, and estimates of the numerical change to confidence intervals and UCL values that would result if alternative assumptions that OEHHA agrees are reasonable were made instead.*

Q19.5 *Does OEHHA agree that the justification for its assumption that relative risk increases linearly with exposure duration should be clearly stated in the report and that the public should be given a chance to comment on it? Do they agree that justification (if any) for this critical assumption is not adequately presented in the current draft? (The background for this question is that this assumption, presented without apparent justification or critical discussion by OEHHA, critically drives the numerical outcomes of their risk assessment.)*

Q19.6 *Does OEHHA agree that there is some probability that relative risks do not increase linearly with duration of exposure? If so, how do they believe this possibility should be reflected in their risk assessment? (It is not currently reflected.)*

Q20. Figure 7-3 (p. 7-54) assumes that "Attained age and calendar year are linear and quadratic continuous covariates". OEHHA further states (p. 7-26) that "The current analysis explored the fit and other characteristics of a number of forms of a general model. The model that appears to be most satisfactory is the one with linear and quadratic continuous covariates, age and calendar year."

Q20.1 *What is OEHHA's criterion for selecting a "most satisfactory" model? (In Appendix D they refer to the AIC and BIC, but not to other criteria such as cross validation. Also, in Appendix D, they consider only a narrow range of parametric models for these criteria to compare, excluding various low-dose non-linear models that we would expect to be much more "satisfactory" by any objective measure, including AIC and BIC.) Have other authoritative bodies accepted this criterion in preference to all others? Would different, equally valid criteria lead to different choices of models? If so, how is this uncertainty reflected in OEHHA's risk calculations?*

Q20.2 *Does OEHHA recognize that, when the correct parametric family of models is unknown, there may not be a single "most satisfactory" model to use. Do they agree that Bayesian model-averaging with a wide variety of candidate*

models may then out-perform any single model according to nearly any objective evaluation criterion? Is OEHHA willing to apply a model-averaging approach instead of a model selection approach, in order to improve accuracy, reduce model-selection bias (discussed next), and improve characterization of uncertainty by incorporating model uncertainty?

Q20.3 Does OEHHA recognize that using data to select among alternative models (e.g., using AIC or BIC with finite sample sizes), as they have done, creates a model selection bias (see e.g., Urban Hjorth, 1994, reference previously supplied to OEHHA?) Do they agree that they have not discussed or corrected for this bias (e.g., using cross model validation) in their risk calculations and calculation of confidence intervals?

Q20.4 Does OEHHA recognize that using data to select among alternative models as they have done leads to incorrectly narrow confidence intervals for model predictions? (See e.g., Urban Hjorth, 1994.) Do they concede that, were they to widen their estimated confidence intervals to correct for this effect, the lower confidence limit of 0.0043 cited on page 7-26 might well fall below zero (i.e., the estimated excess risk per year of exposure would no longer differ significantly from 0?)

Q20.5 Is OEHHA willing to withdraw its estimates of confidence intervals until it has made a correction for model selection bias (e.g., using cross validation)? (If not, are they at least willing to state in their report that they are using biased estimates with confidence intervals that are artificially narrow?)

Q20.6. Does OEHHA agree that other model forms, at least as plausible and that fit the data at least as well as the forms they have selected, could give different risk estimates? Does OEHHA agree that this possibility should be reflected in its stated range of plausible risk values? (This question reflects the concern that what OEHHA refers to in Appendix D as a "general model" is not truly general; there are many plausible exposure-response curves that cannot be reproduced by selecting parameter values in their allegedly "general" model.)

Q20.7 Does OEHHA agree that their "general model" in Appendix D is not truly general, in the sense that it cannot represent any arbitrary smooth function relating the dependent variable to the independent variables? Does OEHHA recognize that such truly general models exist and are used by statisticians (e.g., for "model-free curve fitting"?) Are they willing to withdraw the use of the misleading term "general model" and/or replace their current parametric models with a truly general one? (We have previously supplied OEHHA with relevant technical references. The motivation for this question is a concern that none of the specialized parametric models considered by OEHHA allows the true interaction between attained age and birth year to be expressed. The key role of this interaction is examined next.)

Q20.8.1 Does OEHHA agree that, similar to previous findings by Garshick, effects of attained age on lung cancer risk may differ among cohorts born in different years? Do they agree that their selected risk models do not allow for age effects to vary flexibly (e.g., non-monotonically) between birth-year cohorts? [Some of OEHHA's models such as #11, p. D-5, do consider the possibility of such interactions, but only for one very specialized (multiplicative) algebraic form of interaction. In any case, models with interactions were not used for OEHHA's main risk estimates.]

Q20.8.2 Does OEHHA agree that allowing for more flexible, potentially more realistic models of interactions between attained age and birth year may lead to a finding of substantially reduced risk estimates and/or no exposure-related increase in risk with duration of exposure? [If not, on what basis do they refuse to recognize this possibility, especially given that Garshick has reported that allowing age effects to vary within birth cohorts eliminates the apparent trend of lung cancer risk increasing with exposure duration? Similarly, Cox (1997), using very different "model-free" techniques, also found that allowing for nonlinear, non-multiplicative interactions between birth-year and age at death (or year of death) completely removed any systematic tendency for lung cancer risk to increase with DE exposure concentration or duration. Hence, we believe that OEHHA's failure to also eliminate this trend results from improper modeling of the interaction between attained age, year of birth, and lung cancer risk.]

Q20.9 More generally, does OEHHA agree that different, equally valid approaches to modeling the interactions among covariates might remove the apparent association between DE exposure and lung cancer risk? Do they further agree that this possibility has not been adequately addressed in their chapter 6 (in assessing biases and causation) or chapter 7 (in assessing risk)?

Q21 OEHHA assumes (7-22) that "The equivalent exposure duration for non-continuous exposure is scaled on the basis of volume of air breathed." What biological justification can be provided for this assumption, for DE health effects? We believe it is more plausible to assume that an intermittent exposure pattern that allows the lung to clear itself and repair cell damage between successive exposures is likely to be less-than-proportionally hazardous compared to an exposure scenario without such intermittency. Does OEHHA agree that this is possible and a reasonable assumption? Do they agree that it could reduce risk estimates? (If so, how should their current range of risk estimates be changed to reflect the less-than-proportional hazard from intermittent compared to non-intermittent exposures? If not, then what physiological evidence does OEHHA offer to support its assumption that giving a person time between exposures creates no risk-reducing effect other than reduction in exposure?)

Q22 OEHHA (p. 7-23) defines lifetime unit risk as " The probability of lung cancer at the target age in the table modified by exposure less the probability at the same age in the original table."

Q22.1 Does OEHHA agree that competing risks (i.e., other possible sources of lung cancer) must be taken into account in order to calculate the cause-specific hazard function for the incremental risk due to DE? Do they agree that they should be (and have claimed to be) calculating a cause-specific hazard function for DE?

Q22.2 It is not clear to us what kind of cause-specific hazard function for lung cancer due to DE exposure OEHHA has attempted to calculate.

Q22.1 Is the cause-specific risk attributed to DE exposure in OEHHA's calculations intended to represent a net risk, a partial crude risk, or something else?

Q22.2 Whatever the answer to Q22.1, what specific formula was used to calculate the DE-specific hazard function (The description on pages D-4 and D-5 is too vague to allow us to understand and replicate exactly what was done.) Does the formula used agree with any generally accepted definition of cause-specific risk? If so, please provide the definition and a specific reference (page number and equation number, if possible.) (The motivation for this question is that it appears to us, based on the description on pages D4 to D-5, that OEHHA has used an incorrect procedure for calculating the cause-specific risk for DE exposure. We would like to obtain enough detail to check this.)

Q22.3 Does OEHHA acknowledge that unique cause-specific hazard functions cannot be identified from the available lifetime data on estimated DE exposures and lung cancers? (This is due to the "identifiability problem" for cause-specific hazard functions in competing risk models; see e.g., Kalbfleisch and Prentice, *The Statistical Analysis of Failure Time Data*, Wiley, 1980, especially section 7.2.5.)

Q22.4 How, if at all, has OEHHA overcome the identifiability problem for cause-specific hazard functions?

Q22.5 Kalbfleisch and Prentice (op cit, p. 177) state that "Detailed knowledge of the biological or physical mechanism giving rise to failure [e.g., lung cancers] as well as knowledge of the biological or physical mechanisms giving rise to the removal of certain failure types [e.g., DE-associated lung cancers] would usually be required in order to estimate failure rates of certain types, given that the possibility of other causes has been removed." Does OEHHA agree that such detailed knowledge of the biological mechanisms of lung cancer causation with and/or without DE exposure is not yet available? If so, how do they justify their

approach to defining and estimating cause-specific risks of lung cancer attributable to DE?

Q23 OEHHA states (p. D-6) that "All the results presented for these general models assume a 5-year lag from carcinogenesis to death. This is the lag found by Garshick *et al.* (1988) to give a significant trend of relative hazard with cumulative exposure."

Q23.1 *Does OEHHA agree that searching for the lag to use in order to maximize the statistical significance of a trend creates a multiple-hypothesis testing bias unless p values are adjusted downward?*

Q23.2 *Does OEHHA agree that the estimated trend of lung cancer risk with exposure duration is expected to be biased upward and that the estimated significance level is biased downward by this procedure of searching for a results-maximizing lag?*

Q23.3 *Does OEHHA agree that using a single lag of 5 years for the lung tumor-to-death latency period in all individuals with lung cancer understates the true variability in latency periods? Do they agree that omitting this variability leads to different risk estimates and confidence bands than would be obtained if this source of variability were included in the risk modeling?*

Q23.4 *Does OEHHA recognize that its use of a single lag for all individual customers is a simplification that leads to biased estimates for the other model parameters? Can they put a useful bound on the extent of this bias, perhaps using the SIMEX procedure (references previously provided?)*

Q24. OEHHA states (p. D-8) that "The use of the Armitage-Doll form of the multistage model... is based on accepted mechanisms of carcinogenesis..."

Q24.1 *Does OEHHA agree that the Armitage-Doll form is not based on mechanisms of carcinogenesis that are generally accepted for DE (as opposed to other chemicals)? (We and others believe that the rat data and mechanisms of tumorigenesis provide an adequate basis for challenging the routine application of the Armitage-Doll model to DE.)*

Q24.2.1 *Does OEHHA agree that the form of the multistage cancer risk model they have used (bottom of page D-8) is only a mathematical approximation that is not guaranteed to be accurate for relatively common tumors (e.g., lung cancer)?*

Q24.2.2 *Does OEHHA agree that this approximation can, in principle, over-state the true risk by arbitrarily large factors? Do they further agree that, in practice, the approximate formula they are using does substantially over-state risks for*

many chemicals? (This question is motivated by the following mathematical issue. Suppose that all of the coefficients and terms in the formula are positive. Then, let any of the a-coefficient values approach infinity, meaning that the corresponding transition is expected to happen quickly. Then the approximate model used by OEHHA implies that $h(t)$ must also approach infinity, meaning that the tumor probability approaches 1. But in reality, having one transition take place very quickly only means that another transition rate will become rate-limiting. If the rate-limiting transition rate is small, the lifetime probability of tumor will also be small, despite the fact that the approximate formula predicts it will approach 1. For further details, see the working paper "A comparison of regulatory implications of traditional and exact two-stage dose-response models" by W.A. Chiu et al., Department of Physics, Princeton University.)

Q24.2.3 *Will OEHHA agree to retract risk estimates based on the approximate model at the bottom of page D-8 and use risk estimates based on exact (non-approximate) analysis instead? (If not, will they at least provide a quantitative estimate and explanation of by how much the approximate formula is expected to over-estimate the true risk as calculated from the exact form of the model?) Our concern here is that the approximation being made is unacceptably inaccurate and can lead to large overstatements of risk.*

Q25 OEHHA states (p. 7-24) that "From the odds ratio for 20 yr duration of exposure, the coefficient of increase with duration of exposure by (sic) assuming a linear rise over 20 years." (We assume they mean "was estimated by assuming a linear rise.")

Q25.1 This description is too vague to let us understand and replicate OEHHA's calculations. *Do they mean that they used only the data corresponding to a 20-year duration of exposure (thus excluding the rest of the data)? If so, on what grounds did they exclude the remaining data?*

Q25.2 *Does OEHHA agree that assuming a linear rise over 15 years or over 25 years would be just as valid as assuming a linear rise over 20 years? Do they agree that making different, equally valid, assumptions about the length of the linear rise would change their estimated slopes and give significantly smaller risk estimates (especially if longer durations than 20 years are used)?*

Q25.3 *On what grounds does OEHHA justify the assumption of a linear rise? Surely, the rat data make it plausible that a nonlinear rise with a sharp increase after a long, flat initial segment would be at least as plausible as a linear rise.*

Q25.4 *Does OEHHA agree that reasonable changes in their "linear rise" assumption (e.g., assuming a linear rise over some other number of years, or assuming a non-linear rise) could reduce estimates of lung cancer risk? Do they*

agree that such changes could produce confidence intervals for the slope coefficient that include zero?

Q26 OEHHA states (p. 7-27) that "Background concentration is subtracted from all measured concentrations so that the unexposed workers have zero concentration."

Q26.1 *Does OEHHA agree that the background concentrations for individual workers are not known?*

Q26.2 *Does OEHHA agree that the background concentrations for individual workers are expected to differ for different workers?*

Q26.3 *In light of these points, does OEHHA agree that subtracting estimated average background concentration does not, in fact, have the effect of assigning zero concentration to individual unexposed workers, but instead adds a random component to their estimated background concentrations?*

Q26.4 *Is OEHHA aware that their subtraction of a single estimated average background concentration is expected to bias their risk estimates? Have they tried using SIMEX or other techniques to remove this bias (and, if so, which techniques?) If not, how should their risk estimates be adjusted to control for the bias introduced by subtracting estimated average background concentration?*

Q27 OEHHA states (p. 7-28) that "Subject to many uncertainties... the range of 95% UCL for unit risk for the Garshick *et al.* cohort data is 1E-4 to 1E-3." However, this range of uncertainties does not incorporate or reflect the many uncertainties that OEHHA then lists..

Q27.1 *Does OEHHA acknowledge that the presented range of unit risk UCL does not, in fact, include the "many uncertainties" referred to in Section 7.3.5? (For example, it does not indicate the quantitative impacts of low-dose nonlinear vs. low-dose linear model uncertainties, nor the effects of data uncertainties, other modeling assumptions, model selection bias, or exposure uncertainties.)*

Q27.2 *Does OEHHA agree that its presented range of 95% UCL values must be widened to reflect the "many uncertainties" that they have acknowledged and discussed verbally in Section 7.3.5, but have not yet quantified or included in their quantitative presentation of the range of uncertainties?*

Q27.3 *Does OEHHA agree that, after the "many uncertainties" referred to are taken into account, it may prove to be the case that it is "reasonable and very likely" that the confidence limits on excess risk at low doses include zero?*

Q27.4 *Does OEHHA acknowledge that nothing in the quantitative risk assessment they have presented specifically quantifies risk due to DE exposure as opposed to risk due to other workplace exposures (presumably to a mix of carcinogens?) How does OEHHA justify attributing the risk due to workplace exposure specifically to DE, rather than to competing risks?*

Q28 OEHHA states (p. 7-28) that "Theories of carcinogenesis for a cancer that has a substantial background, as does lung cancer, suggest that the risk would not generally have a threshold..." *Does OEHHA agree, and will they stipulate in their report, that the theories they refer to were not developed specifically with reference to DE and may not apply to DE (e.g., if the mechanism of lung cancer induction by DE turns out to be solely a high-dose phenomenon)?*

Q29 OEHHA states (p. 7-31) that "The current results use one simple linear relationship to characterize a gross overall effect. The form of the model and the assumptions about data selection are uncertain."

Q29.1 *Does OEHHA agree that the uncertainties they refer to here have not been incorporated into the range of quantitative risk estimates they have provided?*

Q29.2 *Does OEHHA agree that the risk estimates and slope parameters for specific individuals may be far smaller (perhaps zero for some individuals) than the "gross overall effect" they have estimated would indicate? (If not, on what specific grounds do they reject this contention of heterogeneity in individual risks?)*

Q30 OEHHA begins its conclusions section (p. 7-35) with the phrase "Based on the human data..." We believe this is misleading. Instead, "Based on the human data and on numerous untested assumptions about exposure, risk models, selection of subsets of data, etc." would more accurately convey the analysis that has been done. It would also more fully reflect the multiple sources, not all of them based on solid data, that contribute to OEHHA's final range of quantitative risk estimates. *Will OEHHA agree to state in its report that a wider range of UCL values would result if the reported range were revised to account for model uncertainties, exposure assumption uncertainties, data uncertainties, uncertainties about causation, and other uncertainties that OEHHA has listed but not addressed quantitatively?* It is particularly important to us that the report should mention that some reasonable models and assumptions could lead to the conclusion that the plausible range of UCL values should include zero (e.g., models that have smooth exposure-response relations with a slope of zero at the origin.) We believe that such a statement could be relevant to decision-makers and is well justified by the many uncertainties in the analysis.

Q31 OEHHA states (p. 7-35) that "... biologically-based analyses improve the unit estimates of risk." We believe that the phrase "biologically-based analyses" is misleading here. It is usually used to mean physiologically-based pharmacokinetic and/or pharmacodynamic models. No such models have been developed or used for DE in the current draft. *Will OEHHA agree to drop the phrase "biologically-based analyses" from this passage?*

Q32 OEHHA states (p. 7-36) that "there is a consistent small increase of relative lung cancer risk above 1... The task of quantitative risk assessment in this chapter and Appendix D is to provide reasonable estimates of the human risk." Given that only association, and not causation, has so far been demonstrated, *does OEHHA agree that the range of "reasonable estimates of the human risk" known to be caused by DE exposure should include zero? Will they accordingly modify their reported range of risk estimates to include zero? If not, on what objective grounds do they exclude zero as a reasonable and likely value for the excess risk of lung cancer caused specifically by DE exposure?* (Our concern here is that the risk assessment seems to pass from association to causation without warning the reader of the important distinction. We also believe that zero is the single most likely value for the slope of the exposure-response relation at the origin, based on our independent statistical analyses of the rat and human data.)

Q33 OEHHA presents results of risk estimates based on rat data on page 7-36.

Q33.1 *Will OEHHA add a statement that rats show no direct evidence (i.e., not based on modeling) of increased risk at the lowest concentrations?*

Q33.2 *Will OEHHA add a statement that they have not used (or tested, e.g., via AIC and BIC, the comparative merits of using) risk models that are able to indicate increased risks at high doses but not at low doses?*

Also, although OEHHA has already responded that it refuses to disaggregate the male and female rat data for purposes of risk modeling, we request that they at least display this data, so that readers can judge for themselves whether the data in either sex supports OEHHA's assumptions of no threshold and linearity.

BIOAVAILABILITY OF THE ORGANIC FRACTION OF DIESEL EXHAUST

in the ARB/OEHHA Draft Report

**on the
"Proposed Identification of Diesel Exhaust
as a Toxic Air Contaminant"
February 23, 1998**

Review Comments

by

**Engine Manufacturers Association
Chicago, Illinois**

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March 26, 1998**

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OEHHA attributes genotoxic role to exhaust or diesel particles without recognizing that organics must be first extracted by solvents and concentrated before the mutagenic action can be demonstrated.

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OEHHA uncritically accepts the unrealistic character of in vitro experiments using diesel exhaust concentration gradients that cannot be translated into in vivo exposures

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OEHHA uses solvent extracts as surrogates of diesel particles without examining the strength of hydrocarbon-particle bonds and without paying attention to the ability of biological fluids to extract hydrocarbons from particles. OEHHA frequently refers to studies that have not been done on genuine diesel particles but on particles with added hydrocarbons that have been eluted by biological fluids.

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4. CONCLUSIONS

5. REFERENCES

1. BACKGROUND

Under legislative mandate of the Assembly Bill 1807, the Air Resources Board is addressing the potential public health effects of air pollutants and evaluates diesel exhaust as a candidate toxic air contaminant under the California air toxics identification program. ARB staff prepared a Technical Support Draft Report that was offered for public comments in May 1997. In commenting on the draft, members of the public argued that the OEHHA draft is scientifically inadequate and falls short in providing adequate evidence from animal studies that diesel exhaust exposure produces lung tumors in laboratory animals by the genotoxic effects of chemical adsorbed on the surface of Diesel particles.

In the response, the OEHHA staff reiterated their strong belief that the genotoxic effects may be involved in the initiation of pulmonary carcinogenesis in humans but failed to provide additional specific data to support this claim. The text insists that:

"...several lines of evidence suggest bioavailability:

First, the in vitro genotoxic activity of diesel exhaust particles dispersed in pulmonary surfactant exhibited similar activity to particulates extracted with dichloromethane.

Second, inhalation exposure of rats and monkeys to diesel exhaust results in DNA adduct formation and in vitro exposure of rat tissues to diesel exhaust induces unscheduled DNA synthesis.

(Third,) DNA adducts have been associated with occupational exposure to diesel exhaust.

Fourth, urinary metabolites of PAH have been found following exposure to diesel exhaust...

.. Preliminary evidence indicates the same might be true for humans. (emphasis added) Consequently, it appears that organic chemical adsorbed onto the particles, particularly the genotoxic components, are likely to be bioavailable in humans." (page C-OEHHA-50, February 23, 1998)

Thus, the OEHHA staff concedes that the actual human evidence is still preliminary and improper to be used in support of identification of diesel exhaust as a Toxic Air Contaminant. More importantly, by disregarding the role of bioavailability of chemicals adsorbed on the surface of particles, the OEHHA continues:

- 1 to attribute genotoxic role to exhaust or diesel particles without recognizing that organics must be first extracted by solvents and concentrated before the mutagenic action can be demonstrated.
- 2 to accept the unrealistic character of in vitro experiments using diesel exhaust concentration gradients that cannot be translated into actual in vivo exposures.
3. to consider solvent extracts as surrogates of diesel particles without examining the strength of hydrocarbon-particle bonds and without paying attention to the ability of biological fluids to extract hydrocarbons from particles.
4. to use studies that have not been done on genuine diesel particles but on particles with added hydrocarbons that have been eluted by biological fluids, and; .
5. to disregard studies reporting that inhalation exposures to Diesel exhaust did not stimulate the activity of hydrocarbon-metabolizing enzymes - as would be expected if organics were bioavailable

Our comments point out additional information that should be considered before the speculative deductions are used for an important regulatory process.

2. BIOAVAILABILITY UNDER PHYSIOLOGICAL CONDITIONS

The issue of bioavailability of organics adsorbed on the surface of Diesel particles deposited in the respiratory airways was raised in 1983 on the basis of pharmacological principles emphasizing that the availability of any drug or compound entering living organism for interacting with body components depends on the solubility of the administered compound in biological fluids, i.e. extracellular fluid and plasma. This solubility is of cardinal importance for the distribution of any compound in the body and for its possibility to reach the target organ, tissue or cell. The experience of pharmacotherapeutics shows that this availability for biological fluids is a basic prerequisite for the manifestation of any physiologic or toxic response in a living organism. When the drug is administered in an insoluble form, no drug will reach the target organ receptors and the expected response will not occur (Vostal, 1983).

Environmental pollutants are entering the organism by many different routes and a strong possibility exists for an adverse effect to occur at the site of the entry. Such a local effect may become the dominant action of the pollutant, but again, the possibility of the pollutant reacting with the immediately adjacent cells is dependent on its solubility in biological media.

2.1 Solubility of Particle-Associated Organics in Biological Fluids

"OEHHA attributes genotoxic role to exhaust or diesel particles without recognizing that organics must be first extracted by solvents and concentrated before the mutagenic action can be demonstrated".

Many questions exist regarding the reality of this approach in predicting the actual effects of diesel exhaust because the organic fraction has to be extracted by solvents from particles and concentrated before it shows mutagenic effects in tests using the Salmonella microsome assay. Difficulties with the detection of trace amounts of polycyclic hydrocarbons in the extract resulted in a controversy regarding the ability of biological fluids to extract hydrocarbons from soot particles in vivo. In the 1980's, Siak et al.(1980) and Brooks et al.(1980) used the same laboratory approach and reported that when fluids compatible with the internal environment of the human body have been tested, mutagenic activity was significantly reduced and represented only a small fraction of the amount reported for the organic extracts.

Parallel studies from other laboratories also reported that organic materials dissociate from particles much more slowly in vivo than when extracted by organic solvents in vitro and that serum and tissue cytosols significantly reduce the cytotoxicity of diesel particle extracts (King et al., 1981, Li et al., 1981). As a result, mutagenic effects obtained by testing the solvent extracts might have falsely indicated diesel particle actions that do not exist in the living organism.

In strong contrast with these observations, OEHHA staff insists that they

"...surveyed diesel exhaust-, diesel exhaust particulate-, and diesel exhaust extract-induced genotoxicity in bacteria , yeast, Drosophila, rodents, non-human primates and humans... Much of the information regarding genotoxicity has been obtained using diesel exhaust particles or extracts of diesel exhaust particles" (Part C-OEHHA-50, February 23, 1998)

By insisting on the relevance of using extracts as a surrogate of diesel exhaust, OEHHA incorrectly attributes genotoxic role to exhaust or diesel particles without recognizing that organics must be first extracted by solvents and concentrated before the mutagenic action can be demonstrated.

The OEHHA is prepared to concede that Siak (1980) as well as Brooks (1980) and King (1981) found little or no mutagenic activity in extracting diesel particles with physiological fluids, but depend in their position primarily on recent findings by Wallace (1987) and Keane (1991). These authors differ from previous studies by dispersion techniques that may better simulate the interaction of inhaled particles with pulmonary surfactant. The methodology differs however only by using sonication at lower temperatures instead of the Soxhlet extractions. By this approach, dichloromethane extraction were less effective and mutagenic effects obtained by extractions with dipalmitoyl lecithin have exceeded the activity of the dichloromethane extract. These results contradict previous findings reporting the inability of pulmonary surfactant to extract any mutagenic activity. However, instead of freshly collected diesel particles, Wallace *et al.* (1987) used aged samples from scrapings of the inside of the exhaust pipe or of filter bags connected to a stationary engine. These sampling conditions of aged samples exposed for a long time to engine exhaust provides an opportunity for secondary artifacts. Under these conditions, Lee *et al.* (1987) found newly formed mutagens, dinitropyrenes, that were not present in the fresh samples collected from same site. These dinitropyrenes, which demonstrate a powerful action in Salmonella bioassays, are formed from 1-nitropyrene by continuing exposures to nitrogen oxides in the dilution tunnel. Because these mutagens are not deposited on particles during the combustion process, they can be readily separated from the soot deposits even by more polar media like dipalmitoyl lecithine (Lee et al., 1987). The point we make here is that by not using the genuine diesel particles, the Wallace study does not simulate the real character of particles formed during the actual combustion process and cannot be used here in the Report to reverse previously reported observations from three independent laboratories.

The OEHHA conclusion that more recent data provide evidence indicating that chemical compounds adsorbed on diesel particles can be released from the particles by the biological media in the respiratory airways is, therefore, based on questionable information and does not support the action of particle extracts as an evidence of this process occurring in the body. The OEHHA staff should reevaluate their position and insist on further verification of the reported data before they are used in support of a regulatory action.

2.2 Unrealistic *in vitro* concentration gradients translated into real world conditions

"OEHHA uncritically accepts the unrealistic character of *in vitro* experiments using diesel exhaust concentration gradients that cannot be translated into actual exposures *in vivo* "

Numerous *in vitro* experiments report that upon direct incubation of high doses of diesel particles with various mammalian cells, in tissue cultures or on plates with inoculated bacteria, evidence of a mutagenic action can be found (Gu et al. 1992 and others). However, OEHHA fails to recognize that direct application of an unusually high concentration gradient does not replicate the actual contact of diesel particles with cells in the human body. Even though that these extreme conditions frequently permit one to observe diesel particle action that would not be manifested by using more realistic lower concentrations, OEHHA should recognize that similar relationships or dose/response conditions cannot be found in the real world.

Because most evidence of genotoxic action of whole diesel particle or exhaust have been obtained either by using concentrated solvent extracts of diesel particles or extremely high concentration gradient (mg mass per ml of media or tissue culture) in direct applications of whole diesel exhaust, the OEHHA should recognize the obvious lack of relevance of these studies for actual conditions that are encountered *in vivo*

after ambient exposures. When the used concentrations are recalculated in terms of the lung surface distribution or distribution in the body fluid, unrealistic accumulation of particulate burdens or mass concentrations would be required that is irrelevant to the actual action of the real environmental concentrations that could ever be anticipated. More importantly, such a situation would never occur because before the genotoxic effects could be manifested, the whole organism would suffer from the general toxicity of the extreme diesel exposures. Because many *in vitro* genotoxic effects are not manifested unless high concentrations are used, OEHHA should critically evaluate the practical relevance of these findings before they are used in support of the proposed regulatory actions.

2.3 Particle-Organic Matter Bonds

"OEHHA uses solvent extracts as surrogates of diesel particles without examining the strength of hydrocarbon-particle bonds and without paying attention to the ability of biological fluids to extract hydrocarbons from particles. OEHHA frequently refers to studies that have not been done on genuine diesel particles but on particles with added hydrocarbons that have been eluted by biological fluids"

In the interpretation of the genotoxic action of particle-associated organics, OEHHA frequently depends on data obtained in studies with particles carrying organics that have been coated on gallium oxide or diesel particles by laboratory techniques (Sun et al, 1982, 1983, 1984, 1988). The text correctly recognizes that the bioavailability of adsorbed organics on particles is determined by:

- (1) the surface structure of the particle,
- (2) the composition of the adsorbed organic compounds,
- (3) the composition of the extracellular and intracellular fluids,
- (4) the balance of the molecular binding between the particles and the adsorbed molecules, and
- (5) the metabolism of the desorbed chemical (OEHHA, page 3-9, February 1988).

The binding energies of the vapor to particle bond are recognized as determining the extent of bioavailability. In spite of these statements, OEHHA uncritically uses data from these experiments for toxicokinetics of organics released from the particle without any documentation that the forces binding the laboratory-adsorbed molecules are identical with those that are responsible for organics deposited on the particle during the combustion process. OEHHA incorrectly accepts these data as fully equivalent to the genuine diesel particles without recognizing that their releases and bioavailability may be quite different.

The artifactual character of the experimental model is clearly demonstrated by the observation that the "initial phase of lung clearance was very rapid with a half-time of clearance of less than one hour" (Sun et al, 1984) when the radioactivity clearance from the lung is plotted as a function of post-exposure time. These rapid elution times sharply contrast with the *in vitro* extraction of organics from diesel particles that require minimally four hours of contact with a highly non-polar solvent at an elevated temperature. In fact, the rapid removal of the radioactive marker from the particles is more similar to disposition of benzo(a)pyrene after administration of pure aerosol than to any indicator of the organics-elution from the "genuine" diesel particles.

The failure of the used surrogate to simulate the dissolution of organics from the genuine diesel particles *in vivo* seriously questions the proposed inclusion of an "organic washout" into the model simulating the clearance of diesel organics in the laboratory rat. The uncertainty about the actual strength of the association of organics with particles contradicts the use of "transport rates" derived from these studies for

describing the availability of diesel organics for potential interaction with respiratory cells. Similar conclusions apply to studies using radioactively labeled 1-nitropyrene deposited by the same methodology on diesel particles (Bond *et al.*, 1986) or on carbon black (Wolff *et al.*, 1989).

In view of these findings, OEHHA should critically reevaluate and modify sections on particle-associated organic compounds, their clearance from the lung, biomarkers associated with diesel exposures and the summary of toxicokinetics (page 3-9 to 3-16) before the data are used for the evaluation of bioavailability of organics from the genuine diesel particles, and certainly before using such questionable findings as support for any regulatory action.

2.4 Evidence from Animal Bioassays

"OEHHA disregards studies reporting that inhalation exposures to Diesel exhaust did not stimulate the activity of hydrocarbon-metabolizing enzymes - as would be expected if organics were bioavailable"

There is more than adequate evidence in the literature that reaffirms the unavailability or limited release of the particle adsorbed organics *in vivo*. Practically all reports from long-term bioassays fail to indicate any enzymatic or immune response such as would be expected when the hydrocarbons were released into the organism.

Chen *et al.* (1981,1983) investigated the effects of long-term inhalation of diluted diesel exhaust on aryl hydrocarbon hydroxylase activity and cytochrome P450 content in lung and liver microsomes in laboratory rats and compared the findings with intraperitoneal and intratracheal administration of extracts of particle adsorbed organics. During long-term exposures to Diesel exhaust, the study observed a decrease instead of an increase of microsomal hydroxylase activity such as would be expected if the organics were released from the particles into general circulation. In contrast, nearly a two fold increase in aromatic hydroxylase activity occurred when particulate extracts (25-125 mg/kg body weight) were administered intraperitoneally. These doses are 10-15 times larger than the most conservative estimates of the deposited lung burdens. Similar doses (as high as 6 mg extract/kg body weight) were required when extracts were administered intratracheally into the lung. Even in that case, the induction was slow and occurred solely in lung tissue, indicating that diesel particle extract does not absorb easily into the lung circulation and is not distributed to other organs.

These data suggest that the lack of enzyme induction in rats exposed to whole diesel exhaust by inhalation is either due to unavailability of particle-adsorbed hydrocarbons for a release from the particles or by their presence in the body in insufficient quantities for enzyme induction. Identical results were reported by other laboratories (Navarro *et al.*, 1981).

No immune responses of the lymphoid tissue to diesel particles have also been observed in the lung after long-term exposures in spite of positive responses occurring when particle extracts were intraperitoneally injected (Dziedzic, 1981, 1983).

The absence of *no in vivo* response is consistent with other findings and suggests that:

- (a) diesel particles deposited in respiratory airways are phagocytized by alveolar macrophages and - if not removed by a mucociliary escalator - the macrophages with engulfed particles are rapidly sequestered in macrophage clusters that permit no contact

with extracellular fluids;

- (b) living organisms have no other extracellular mechanisms which can solubilize and elute the hydrocarbons from the surface of particles *in vivo*;
- (c) the phagocytic function of the alveolar macrophages not only prevents a more intimate contact of deposited particles with the sensitive cells of the respiratory system, but is capable of deactivating the biological aggressivity of chemical compounds attached to their surface.

Siak and Strom (1981) studied mutagenic properties of inhaled diesel particles that deposited in the lung of laboratory rats. Pulmonary alveolar macrophages were obtained by bronchopulmonary lavage from exposed animals immediately after exposure and 1, 4, and 7 days thereafter, concentrated by filtration and extracted by dichloromethane. A positive mutagenic effect was detectable only in extracts of macrophages obtained immediately and one day after exposure. Starting with the second day after exposure, there was no mutagenic activity in extracts from macrophages and the TLC fluorescence banding characterizing their presence completely disappeared.

Similarly, Wheeler *et al.*, (1983) incubated *in vitro* macrophages with Diesel particles and observed that the extractable mutagenic activity was reduced in the cells with little or no change in mutagenicity in the extracted media. The authors concluded that the extractable mutagenic hydrocarbons adsorbed on Diesel particles are probably transformed to more polar metabolites prior to their release from the cells.

These studies have been both presented in public meetings and published in the peer-reviewed literature, and no thorough review of available information should avoid discussing them before assessing the diesel induced risks. It is, therefore, disappointing that many of these published and publicly discussed studies are not included in the reference lists of the OEHHA document.

It can be summarized that contrary to the predicted mutagenicity and chemical carcinogenicity of Diesel exhaust (based on testing of particle extracts), experimental evidence finds no involvement of the extractable fraction in the carcinogenic process because:

- (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 were phagocytized by alveolar macrophages;
- (b) 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 organics do not contribute to an increased tumor formation.

3. DNA- ADDUCT FORMATION

"OEHHA fails to recognize the lack of exposure information and the complexity of DNA adducts identification"

3.1 Long-term Exposure in Animals

Gallagher *et al.*, (1994) studied formation of lung DNA adducts derived from polycyclic aromatic hydrocarbons and nitro-PAHs in rats exposed high concentrations of Diesel exhaust, carbon black and titanium oxide for two years. The authors found no increases in total DNA adducts that would be attributed to nitro-PAH constituents present in the diesel particle extracts. In spite of extremely high levels of exposure, no lung DNA increases were found in control, diesel exposed or carbon black and titanium dioxide exposed animals. The only finding was an increase with time for the DNA adducts for the putative "DNA adduct like" I-compounds in control animals which have been shown to be related to age, hormonal status and diet (Randerath, 1992, 1996). Contrary to all expectations, these adduct levels remained at the same level in all exposed animals. Because diesel exposed animals accumulated a large lung burden of retained diesel particles (39.5 mg of organic matter), the lack of DNA adducts formation contradicts the notion of particle-associated hydrocarbon release in the organism.

Mauderly *et al.*,(1994) and Nikula *et al.*,(1995) reported no exposure-specific DNA adduct formation in long-term inhalation experiments in which laboratory rats were exposed to high concentrations of diesel exhaust or carbon black. Only a minor changes have been observed in endogenous DNA adducts that were transiently increased at the start of the exposures.

Contrary to all predictions, inhalation studies have shown that the reaction of particle-associated hydrocarbons with DNA leading to the formation of DNA-adducts is no longer valid because the formation occurs even after carbon black (with no organic fraction) exposures and is detectable in control rats (Randerath *et al.*, 1992). The studies demonstrated "no clear difference in adduct levels over time" (Williams *et al.*, 1992).

Pilot studies on animals exposed to diesel engine emissions have shown inconsistent results finding non-detectable levels of DNA in approximately 50% of animals (Wong *et al.*, 1986). Wolff *et al.* (1990) reported slightly elevated adduct formation in Diesel exposed rats but could not exclude the possibility that oxygen radicals or other reactive agents released from neutrophils and macrophages during the inflammatory response might cause DNA modifications that could be measured as DNA adducts in the post-labeling assay. Increased levels of adduct formation were observed even after carbon black exposures that do not have organics adsorbed on their surface.

It can be summarized that the expected reactions of the organic fraction with DNA and the formation of DNA-adducts as a mechanism leading to a chemical carcinogenesis have been discredited by showing that DNA adducts occur after carbon black exposures (no organics) and are detectable in control rats. Because lung DNA alterations are presumed to be related to tumor-generating processes, these observations suggest that the underlying mechanisms responsible for the specificity of DNA adducts need to be further investigated before they are used as an evidence of potential cancer risks (Bond, 1993).

3.2 Occupational exposures in humans

Hemminki *et al.*, (1994) studied aromatic DNA adducts in circulating lymphocytes obtained from personnel servicing and loading diesel vehicles. The exposed group was represented by non-smoking mechanics who overhauled buses and had skin exposure to lubricating oils, or garage personnel who washed and refueled buses with potential inhalation exposure to diesel exhaust. Electricians and store workers served as a control group. Lymphocyte DNA adducts were elevated in garage workers, bus maintenance workers and diesel forklift drivers. The elevations were however at the borderline of statistical significance and raise the question whether occupational exposure to diesel exhaust was responsible for these marginal elevations of lymphocytes, that could not be answered.

Hou *et al.*, (1995) tested lymphocyte DNA adducts along with hprt mutant frequency and the worker's capability to detoxify foreign compounds in the same non-smoking occupationally exposed group. No difference in mutant frequency was observed between exposed and control individuals. The adduct formation was only marginally correlated with mutant frequency ($r^2 = 0.127$), and no differences were observed in the detoxification rates between different job classifications. Again, the lack of information on exposure did not permit any correlation of the findings with diesel exposure.

The work by Nielsen *et al.*, (1996) examined a similar occupational group of non-smoking workers at the Copenhagen bus terminals. Differences were found between the garage workers and controls in DNA formation and two other biomarkers, i.e. hemoglobin adducts and 1-hydroxy pyrene in urine, but the elevations were small. More importantly, the real source of genotoxins was unclear and other sources of exposure such as skin contact with lubricating oils could not be excluded. Kanoh *et al.*, (1992) have tried to use urinary 1-hydroxypyrene as a biomarker of exposure to hydrocarbons in schoolchildren of three polluted areas of Tokyo. Although differences have been found between schoolchildren from the three districts, it was not clear whether the differences represent dietary or inhalation exposures.

The most recent study (Qu *et al.*, 1997) measured DNA adducts in miners from two diesel-equipped mines and attempted to evaluate differences between pre- and post- occupational exposure differences. Approximately 50% of the workers were active smokers or ex-smokers. Linear regression modeling showed a positive association between adduct and smoking status (smokers had 37% higher adducts than non-smokers) and a negative association of adduct formation with the time on job. No significant association was found between adducts and smoking or adducts and job categories in the second mine. Adduct levels of miners and drivers were approximately 50% higher than in the control group, but differences were not significant. Approximately 38% increase was observed between pre- and post-exposure readings in the first mine and 31% in the second mine.

In general, inconsistent data from the recent studies show that it is premature to make more definitive conclusions on the public health significance of the adduct findings. In fact, there are many unresolved factors that concern the detection of DNA adducts in exposed populations:

1. First, nearly all data were obtained on changes in disposable circulating cells that are not considered the target for diesel particle effects, and are influenced by many variable factors such as diet, intensive physical work and other factors.
2. The role of smoking is particularly important since the active smoker inhales concentrations of organic combustion product that are in excess of any potential environmental or occupational exposures. The opinions about the significance of smoking are controversial. Linear associations have been reported between lung or airway adduct levels and in smoking (Phillips *et al.*,

1988a,b). Elevated lymphocyte adducts are higher in smokers than in non-smokers, but no correlation exists between DNA adducts and consumption of cigarettes (Phillips *et al.* 1990). In addition, large inter-individual variability in the presence of DNA adducts was found in smokers and even larger differences are reported in the lymphocyte adducts (Santela, 1992).

3. Methodological differences in adduct detection and identification make direct comparing of individual studies extremely difficult; and;
4. Mammalian cells contain non-specific DNA modifications, called I- (indigenous) compounds that accumulate in tissues of unexposed animals and are readily detected by post-labeling methods.(Randerath *et al.*, 1987). These I-compounds originate from normal nutrient and intermediary metabolism, show a large chromatographic diversity and demonstrate species-, strain-, tissue-, gender- and diet-dependent profiles (Randerath, 1996, Randerath, 1993).

These factors, particularly the confounding presence of I-compounds, characterize the identification of specific, exposure-related adducts as a very complex problem and make more exact interpretation of sometimes largely different findings difficult. In fact, the complexity of these processes characterizes the use of post-labeling methods and mainly, their interpretation as a very difficult problem at the present time.

4. CONCLUSIONS

Numerous studies demonstrated that the mutagenic activity of Diesel particles was: (a) minimal or negative when tested in extracts obtained with biological fluids; (b) substantially dependent on the presence of high levels of nitroreductase enzymes that are not present in mammalian cells, and; (c) disappeared completely 48 hours after Diesel particles had been phagocytized by alveolar macrophages. In addition, long-term animal exposures to Diesel particles did not induce the activity of hydrocarbon-metabolizing enzymes or specific adverse immune responses - as it would be expected if the particle-adsorbed chemicals were involved in Diesel action - unless solvent extracts of diesel particles were directly administered to animals in doses that highly exceed the levels of public exposures.

The mutagenic and carcinogenic compounds are firmly attached to diesel particles, minimally soluble in biological fluids and are not easily available for transfer into adjacent tissues or the systemic circulation. Testing of the separated extracts *in vitro*, therefore, provides no useful information on the *in vivo* biological activity of diesel particles deposited in the lung. Neither the *in vitro* data nor the use of added markers results can serve as valid predictors of the potential adverse effect of inhaled concentrations of Diesel exhaust or as a meaningful basis for dosimetric models or hazard assessments of inhaled diesel emissions.

OEHHA should recognize that in contrast with the demonstrated genotoxicity of Diesel particle extracts, experimental evidence fails to confirm major involvement of the extractable fraction in the carcinogenic process because:

- (1) Only laboratory-prepared extracts of Diesel particles contain mutagenic compounds, but these extracts are not easily available in *in vivo* conditions. The observed mutagenicity is minimal or absent when tested in extracts obtained with biological fluids, and disappears completely 48 hours after Diesel particles were phagocytized by alveolar macrophages. Moreover, whole Diesel particles are not genotoxic in laboratory tests.
- (2) Adduct formation reported in the literature is not specific for Diesel particles or their extractable organic fraction and cannot be used as evidence of a primary genotoxicity of Diesel exhaust,
- (3) 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 increased tumor formation. These comparative experiments reaffirm that the non-specific particle burden is the principal - if not sole - cause of lung tumor in laboratory rats.
- (4) If the formation of Diesel-induced tumors in laboratory rats is to be adequately described, the risk assessment methodology should reject the unsupported assumptions of a role of organics in the tumor formation and restrict the tumor causality to non-specific effects of accumulated particles. The contributing role of organics is not supported by experimental data, and the continuing association of organics with the causality of Diesel neoplasia in laboratory rats could seriously distort the reality of the final risk estimates.

4. REFERENCES

- Bond, J.A., Sun, J.D., Medinsky, M.A., Jones, R.K. and Hsu C. Yen, 1986. Deposition, Metabolism and Excretion of 1-¹⁴C-Nitropyrene and 1-¹⁴C-Nitropyrene Coated on Diesel Exhaust Particles as Influenced by Exposure Concentration. *Tox. Appl. Pharmacol.*, 85:102-117
- Bond, J., 1993. DNA Adducts. In U.S. EPA Research Needs for Risk Assessment of Inhaled Particulate Matter, Publ. EPA/600/R-93/104, Office of Health and Environmental Assessment, Washington, DC, June 1993
- Brooks, A.L., Wolff, R.K., Royer, E.E., Clark, R., Sanchez, A. and R.O. McClellan, 1980. Biological Availability of Mutagenic Chemicals Associated with Diesel Exhaust Particles, in Peipelko, W.E, Danner, R.M. and A.N. Clarke, Eds.: *Health Effects of Diesel Engine Emissions*, vol 1., EPA Publ. 600/9-80-057a, pp. 345-358
- Chen, K.C. and Vostal, J.J. ., 1981. Aryl Hydrocarbon Hydroxylase Activity Induced by Injected Diesel Particulate Extract vs. Inhalation of Diluted Diesel Exhaust. *J. Appl. Toxicol.* 1;127-131
- Chen, K.C. and Vostal, J.J., 1983. Aryl Hydrocarbon Hydroxylase Induction in Pulmonary Alveolar Macrophages by Inhalation Exposure to Diesel Exhaust Particulates. *Drug and Chemical Toxicology*,
- Dziedzic, D., 1981. Differential Counts of B and T Lymphocytes in the Lymph Nodes, Circulating Blood and Spleen after Inhalation of High Concentrations of Diesel Exhaust. *J. Appl. Toxicol.*, 1:11-115
- Dziedzic, D., 1983. Functional Response of Lymphocytes after Exposure to Diesel Exhaust Materials. Presented at the Society of Toxicology meeting, Las Vegas, NV, March 6-10, 1983, *The Toxicologist* 3:(No.1):8 (GM Research Report GMR-4295)
- Gallagher, J., Heinrich, U., George, M., Hendee, L., Phillips, D.H., Lewtas, J., 1994. Formation of DNA adduct levels in rat lung following chronic inhalation of diesel emissions, *Carcinogenesis*, 15:1291-9;
- Gu, Z.W., Thong, B.-Z., Nath, B., Whong, W.Z., Wallace, W.E., Png, T., 1992, Micronucleus induction and phagocytosis in mammalian cells treated with diesel emission particles, *Mutat. Rresearch*, 279:55-60;
- Hemminki, K., Soderling, J., Ericson, P., Norbeck, H.E. Segerback, D., 1994, DNA adducts among personnel servicing and loading diesel vehicles, *Carcinogenesis*, 15:767-769;
- Hou, S., Lambert, B., Hemminki, K., 1995, Relationship between hprt mutant frequency, aromatic DNA adducts and genotypes for GSTM1 and NAT2 in bus maintenance workers, *Carcinogenesis*, 16:1913-1917;
- Kanoh, T., Fukuda, M., Onozuka, H., Kinouchi, T., Ohnishi, Y., 1993, Urinary hydroxypyrene as a marker of exposure to polycyclic aromatic hydrocarbons in environment, *Environ. Research*, 62:230-241;
- Keane, M.J., Xing, S.-G., Harrison, J.C., Ong, T., Wallace, W.E., 1991, Genotoxicity of diesel exhaust particles dispersed in simulated pulmonary surfactant, *Mutat. Research*, 260:233-238;

- King, L.C., Kohan, M.J., Austin, A.C., Claxton, L.D. and J. Huising, 1981
 "Evaluation of the Release of Mutagens from Diesel Particles in the Presence of Physiological Fluids",
Environ. Mutagenesis, 3:109-121
- Li, A.P., 1981. Antagonistic Effects of Animal Sera, Lung and Liver Cytosols and Sulfhydryl
 Compounds on the Cytotoxicity of Diesel Exhaust Particle Extracts, *Toxicol. Appl. Pharmacol.*, 57:55-62
- Mauderly, J.L., Snipes, M.B., Barr, E.B., Bechtold, W.E., Belinski, S.A., Henderson, R.F., Mitchell,
 C.E., Nikula, K.J. and D.G. Thomassen, 1991
- Mauderly, J.L., Snipes, M.B., Barr, E.B., Belinski, S.A., Bond, J.A., Brooks, A.L. et al., 1994,
 Pulmonary Toxicity of inhaled diesel exhaust and carbon black in chronically exposed rats, Part 1.
 Neoplastic and non-neoplastic lung lesions, Research Report No. 68, Health Effects Institute, Cambridge,
 MA, October, 1994;
- Navarro, C., Charboneau, J. and McCauley, R., 1981. The Effect of In Vivo Exposure to Diesel
 Exhaust on Rat Hepatic and Pulmonary Microsomal Activities. *J. Appl. Toxicol.*, 1:124-126
- Neal, J., Thornton, M. and C.A. Nau, 1962. Polycyclic Hydrocarbon Elution from Carbon Black and
 Rubber Products, *Arch. Env. Health*, 4:598-606
- Nielsen, P.S., Andreassen, A., Farmer, P.B., Ovrebo, S., Autrup, H., 1996, DNA and hemoglobin
 adducts and urinary 1-hydroxypyrene as markers of exposure, *Toxicol. Lett.*, 86:27-37;
- Nikula, K.J., Snipes, M.B., Barr, E.B., Griffith, W.C., Henderson, R.F. and J.L. Mauderly, 1992.
 Influence of Particle-Associated Organic Compounds on the Carcinogenicity of Diesel Exhaust, Annual
 Report of the Inhalation Toxicology Research Institute 1991-1992, Lovelace Biomedical & Environmental
 Research Institute, Albuquerque, NM, December 1992, pp. 105-107
- Nikula, K.J., Snipes, M.B., Barr, E.B., Griffith, W.C., Henderson, R.F., Mauderly, J.L., 1995,
 Comparative pulmonary toxicities and carcinogenicities of chronically inhaled diesel exhaust and carbon
 black in F344 rats, *Fundam. Appl. Toxicol.*, 25:80-94;
- Phillips, D, Hewer, A., Muttin, C.N., Garner, R.C. and King, M.M., 1988a. Correlation of DNA adduct
 levels in human lung with cigarette smoking, *Nature*, 336, 790-792.
- Phillips, D, Hemden, K., Algren, A., Hewer, A. and Grover, P.L., 1988b, Monitoring occupational
 exposure to carcinogens detected by ³²P-postlabeling of aromatic DNA adducts in white blood cells from
 iron foundry workers, *Mutat. Research*, 204: 531-541;
- Phillips, D., Schocket, B., Hewer, A., Bailey, I., Kostic, S. and Vincze, I., 1990, Influence of cigarette
 smoking on the levels of DNA adducts in human bronchial epithelium and white blood cells,
International Journal of Cancer, 46: 569-575;
- Qu, S.-X., Leigh, J., Koelmeyer, H., Stacey, N.H., 1997, DNA adducts in coal miners: association with

exposures to diesel engine emissions, *Biomarkers*, 2:95-102;

Randerath, E., Zhou, G-D, and Randerath, K., 1996, Organ-specific Oxidative DNA damage associated with normal birth in rats, *Carcinogenesis*, 17: 2563-2570.

Randerath K., Li, D., Nath, R. and Randerath, E., 1992, Exogenous and endogenous DNA modifications as monitored by ³²P-postlabeling: relationships to cancer and aging. *Exp. Gerontol.*, 27: 533-549.

Randerath K., Randerath, E., Danna, T.F. and K.L. Putman, 1992. Diesel Exhaust-Induced DNA Damage as Determined by ³²P Postlabeling Analysis. Presented at the 9th Health Effects Institute Annual Conference, Monterey, CA, December 6-8, 1992;

Randerath, K., Zhou, G.-D., Hart, R.W. Turturro, A. and Randerath, E., 1993. Biomarkers of aging: Correlation of DNA I-compounds levels with medium lifespan of calorically restricted and ad libitum fed rats and mice, *Mutat. Research*, 295:, 247-263. c

Santella, R.M., Grono, C., Funts, R.A., Young, T.L., Dickey, C., Singh, V.N., Wang, L.W. and Perera, F.P., 1992, Cigarette smoking related polycyclic aromatic hydrocarbon-DNA adducts in peripheral mononuclear cells, *Carcinogenesis*, 13:2041-2045;

Siak, J.S. and Chan, T.L., 1989. Extractability of the Mutagens on Diesel Particles in Simulated Biological Fluids and Organic Solvents, *J. Appl. Toxicol.*, 26:183

Siak, J.S. and Strom, K.A., 1981. Mutagenicity of Particles in Alveolar Macrophages from Diesel Exposed Animals. Presented at the Society of Toxicology meeting, San Diego, CA, March 1-5, 1981 (GM Research Report GMR 3628).

Sun, J.D., Wolff, R.K. and Kanapilly, G.M, 1982. Deposition, Retention, and Biological Fate of Inhaled Benzo(a)pyrene Adsorbed onto Ultrafine Particles and as a Pure Aerosol, *Tox.Appl Pharmacol*, 65:231-244

Sun, J.D., Wolff, R.K., Kanapilly, G.M, and McClellan, R.O., 1984. Lung Retention and Metabolic Fate of Inhaled Benzo(a)pyrene Associated with Diesel Exhaust Particles. *Tox. Appl. Pharmacol.*, 73:48-59

Sun, J.D., McClellan, R.O., 1984, Respiratory tract clearance of ¹⁴C-labeled diesel exhaust compounds associated with diesel particles as a particle-free extract, *Fundam.Appl.Toxicol.*, 4:388-393;

Sun, J.D., Bond, J.A., Dahl, A.R., 1988, Biological disposition of vehicular airborne emissions: particle-associated organic constituents, In *Air Pollution, the Automobile and Public Health*, Health Effects Institute, Ed., National Academy Press, Washington, DC, pp. 299-322;

Vostal, J.J., 1983. Bioavailability and Biotransformation of the Mutagenic Component of Particulate Emissions Present in Motor Exhaust Samples, *Environ. Health Perspect.*, 47:269-281, 1983

Wallace, W.E., Keane, M.J., Hill, C.A., Xu, J., Ong, T., 1987, Mutagenicity of diesel exhaust particles and oil shale particles dispersed in lecithin surfactant, *J. Toxicol. Environ. Health*, 21:163-171;

Wheeler, C.S. and Vostal, J.J., 1983. Metabolism and Release of Diesel Particle Hydrocarbons by Alveolar Macrophages. Presented at the Society of Toxicology meeting, Las Vegas, NV, March 6-10, 1983 (GM Research Report GMR-4290)

Williams, P.L., Randerath, K., and J.L. Mauderly, 1992

"Statistical Analysis of Correlated Measurements of DNA Adduct Formation in Lungs of F344 Rats Exposed to Diesel Exhaust or Carbon Black", presented at the 9th Health Effects Institute Annual Conference, Monterey, CA, December 6-8, 1992;

Wolff, R.K., Henderson, R.F., Snipes, M.B., Griffith, W.C., Mauderly, J.L., Cuddihy, R.G. and R.O. McClellan, 1987. Alterations in Particle Accumulation and Clearance in Lungs of Rats Chronically Exposed to Diesel Exhaust, *Fundam. Appl. Toxicology*, 9:154-166

Wolff, R.K., Bond, J.A., Henderson, R.E., Harkema, J.R. and Mauderly, J.L., 1990. Pulmonary Inflammation and DNA Adducts in Rats Inhaling Diesel Exhaust Emissions or Carbon Black. *Inhalation Toxicol.*, 2:241-254

Wolff, R.K., Sun, J.D., Barr, E.B. Rothenberg, S.J. and H.S. Yeh, 1989. Lung Retention and Binding of ¹⁴C-1-Nitropyrene when Inhaled by F344 Rats as a Pure Aerosol or Adsorbed to Carbon Black Particles. *J. Tox. Environ. Health*, 26:309-325

Wong, D., Nitchell, C.E., Wolff R.K., Mauderly, J.L. and Jeffrey, A.M., 1986. Identification of DNA damage as a Result of Exposure of Rats to Diesel Engine Exhaust. *Carcinogenesis*, 7:1595-1597