LeVois & Associates

Post Office Box 301
Tiburon, CA 94920

February 10, 1999

Dr. Larry G. Hart
Board Executive Secretary
National Toxicology Program
P.O. Box 12233
Research Triangle Park, NC 27709

Dear Dr. Hart:

Attached are additional comments concerning the NTP's recent reviews of environmental tobacco smoke and diesel exhaust.

Sincerely,

Maurice E. LeVois, Ph.D.
Senior Scientist

Lung cancer risk in relation to exposure to diesel exhaust and environmental tobacco smoke

Maurice E. LeVois, Ph.D.

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Biographical information.

I am the principal scientist in Environmental Health Resources, an association of consulting epidemiologists and statisticians with offices in San Francisco, California. I received my Ph.D. from the University of California, San Francisco in 1984. I was formerly director of the Veterans Administration's Office of Agent Orange Research and Education, and a scientist in the Agent Orange Study unit, Centers for Disease Control. My professional activities have involved the design and conduct of large cohort studies, occupational mortality studies, survey research on problems of artifact in epidemiologic methods, research on cancer incidence and reproductive health effects in populations exposed to agricultural chemicals, epidemiologic modeling and failure analysis of toxic waste management facilities. My curriculum vitae is attached.

I have been asked by the United States cigarette companies to review and comment on two background documents published by the National Toxicology Program (NTP), in which the NTP classifies diesel exhaust as "reasonably anticipated to be a human carcinogen", and classifies exposure to environmental tobacco smoke (ETS) as "known to be a human carcinogen." The views expressed in these comments are my own and not necessarily those of the cigarette industry.

The National Toxicology Program background documents.

The NTP background document on diesel exhaust particulates reaches the conclusion that diesel exhaust is "reasonably anticipated to be a human carcinogen". This conclusion is based upon reports of elevated lung cancer rates in humans occupationally exposed to diesel exhaust, and upon supporting animal and mechanistic studies. It is noted that an increased risk, averaging about RR=1.3, is reported in a majority of human epidemiologic studies, and that higher exposures are associated with higher lung cancer risks in some studies. The report states that the increased risk is not readily explained by confounding by smoking

or asbestos exposure. However, the report notes that the risk cannot always be ascribed to diesel exhaust exposure, and that only some of the studies used "semiquantitative" estimates of exposure, while most studies used inadequate measures of exposure.

The NTP background document on environmental tobacco smoke (ETS) exposure reaches a significantly stronger conclusion—that ETS is "known to be a human carcinogen". The NTP based this conclusion on studies in humans that they say indicate a causal relationship between passive smoking and lung cancer. In these human studies nonsmoker lung cancer rates are compared for groups defined by the smoking status of the spouse, studies of exposure of nonsmokers to ETS in occupational settings, and studies of exposure to parents' smoke during childhood. The background document notes that many spousal smoking studies have reported an increased lung cancer risk, averaging about RR=1.2, with some studies suggesting higher risks with higher exposure. The document also notes that some studies report higher lung cancer risks for occupational groups with ETS exposure, but that there is little or no discernable lung cancer risk from exposure to ETS only during childhood.

For reasons outlined below, I do not believe that there is any significant difference in the strength of the data or consistency of the association between lung cancer and either diesel exhaust or ETS exposure. In both cases the epidemiologic research is simply too inadequate to support a causal inference. Exposure measures employed in both areas are indirect and ambiguous. The weak associations that have been reported in both areas could easily result from very plausible sources of bias and confounding. Such low relative risks are simply below the resolving power of epidemiologic research. Even if all aspects of these epidemiologic study designs were of the highest order of validity and precision, only cautious interpretations could be made. Instead, these studies are based on indirect proxy measures of exposure, often obtained from surrogate respondents, with limited or no data on relevant potential confounders. In addition, likely sources of systematic bias have been introduced by the ETS study design.

PAH exposure.

The diesel exhaust and ETS human studies relied upon by the NTP have important points in common. First, the underlying exposure of concern is essentially the same. In both cases the relevant exposure is to a similar complex mixture of polycyclic aromatic hydrocarbons (PAHs). The list of individual PAH constituents in diesel exhaust and ETS does not differ in any significant way. No single PAH component can account for the possible lung cancer activity of either complex mixture (Bofetta et al, 1997). Exposure of laboratory animals to the gas phase constituents of either tobacco smoke or diesel exhaust has not produced an increase in tumors. The NTP background document indicates a similar range of exposure to respirable particulate matter (RPM) resulting from ETS and diesel exhaust. If anything, the corrected diesel exhaust RPM exposure cited by the NTP (42-224 ug/m^3) is greater than the corrected ETS exposure (15-248 ug/m^3).

Characterization of the extent of exposure.

A second similarity between these two sets of human studies is the method of characterizing exposure. The diesel exhaust studies generally use job titles to classify individuals into more or less exposed study groups. After the primary classification has been made, length of employment in different jobs may be used to arrive at a "semiquantitative" distribution of exposure. Classification of ETS exposure is usually done according to the smoking habits of the spouse. After the primary classification, length of marriage(s) to a smoker, and average amount smoked by the spouse(s) are used to create a "semiquantitative" distribution of ETS exposure. In both the diesel exhaust and ETS studies, no concurrent exposure data are available, and substantial exposure misclassification is likely. Misclassification results in the occupational setting primarily from wide variation in the exact location and ventilation conditions experienced by each individual worker. Likewise, in the ETS studies there is no information about the proximity of the smoking spouse nor is there information on the ventilation conditions that determine individual ETS exposure levels. A notable exception is the study by Kabat, et al. (1995), in which smoker proximity data were collected. I that study closer proximity was not associated with higher lung cancer risk.

The NTP background document is quite clear about the limitations of the diesel exhaust exposure data, stating "...most studies use inadequate measures of exposure." Exactly the same thing has been said

about the ETS studies. The National Research Council's 1986 ETS review noted the presence of data gaps. and weaknesses in the ETS exposure data, in "Summary and Recommendations" sections at the end of several of its chapters. At page 94 the NRC report states "While several individual constituents of ETS have been measured in a number of microenvironments as a proxy for ETS (nicotine, CO, acrolein, etc.), none have met all of the criteria necessary for a suitable proxy, nor has an individual contaminant been uniformly accepted or recognized as representative of ETS exposure." The report goes on to conclude at page 95 that "The limited number of samples, lack of data on the environments where the exposure took place, and lack of a specific proxy for ETS do not permit accurate estimation of the ETS exposure or extension of the data to a larger population."

At page 116 the NRC report goes on to state that "There are problems with self- and proxy reports of ETS exposure inferred from questionnaire responses that limit the utility of these data. The best method by which to estimate individual ETS exposure is not known, and this lack of information hampers all efforts at assessing data quality, including data validity." There has been no change or improvement in the methodology used to assess ETS exposure in spousal smoking studies since the NRC report was published. Clearly, the NTP background document should have noted that ETS studies also "...use inadequate measures of exposure."

Weak associations.

While the ETS background document is silent with respect to difficulties interpreting very weak epidemiologic associations, the diesel exhaust background document does contain a comment that clearly underscores this difficulty. In the first paragraph of section 3.3 of the diesel exhaust background document, an editorial on diesel exhaust research by Silverman (1998) is paraphrased as follows "...the small size of the effect could be due to low levels of exposure, exposure misclassification, or negative confounding, but nevertheless (he) concluded that the effect could not be considered causal because of its small size." The lung cancer/ETS relative risk is even smaller than the diesel exhaust relative risk. Such a weak association clearly cannot be considered causal because of its small size.

Bias and confounding

As noted above, meta-analyses of both diesel exhaust and ETS epidemiologic studies produce very weak pooled relative risks—on the order of RR=1.1 to 1.2 for ETS, and RR=1.3 for diesel exhaust. This fact makes interpretation difficult because uncontrolled bias and confounding could easily account for both weak associations. In the case of diesel exhaust the NTP background document notes that, while not readily explained by confounding due to smoking and asbestos exposure, the increased risk cannot always be clearly ascribed to diesel exhaust exposure. The NTP report notes that the pooled lung cancer relative risk for ETS exposure is even lower than for diesel exhaust, yet the report fails to note that such a weak relative risk cannot always be clearly ascribed to ETS exposure. In fact, several types of bias and confounding have been reported that could account for the weak ETS epidemiologic association (Lee and Forney, 1996; LeVois and Layard, 1995; LeVois and Switzer, 1998).

Diesel exhaust epidemiologic studies have not eliminated the possibility of unequal exposure to other potential lung carcinogens at work, primarily asbestos exposure and exposure to diesel fuel and other workplace chemicals and contaminants. In addition, potential confounders such as unequal cigarette smoking, lifestyle, and dietary risk factors also have not been adequately controlled in the diesel exhaust studies. However, some of the diesel exhaust studies did adjust for smoking, and the nested case-control design used in some of the diesel exhaust studies can be expected to reduce occupational, lifestyle, and dietary differences among study groups.

No ETS epidemiologic study has been able to adequately account for lifestyle and dietary differences because reliable data have not been collected, and the nested study design is not available (Lee and Forney, 1996). The spousal smoking study design virtually guarantees bias related to active smoker misclassification, as well as confounding by dietary and lifestyle exposures that are shared by spouses and differ between smokers and nonsmokers. Both smoker misclassification bias and confounding due to diet and lifestyle can be expected to increase with increasing spousal smoking. Spousal concordance with respect to active smoking is known to increase with higher smoking intensity, leading to a correlation of smoker misclassification and spousal smoking intensity. Similar correlations have been reported in studies of diet, lifestyle, and smoking intensity (Lee, 1992). Thus, the fact that some studies report a weak trend in

lung cancer risk with increasing spousal smoking cannot be taken as unambiguous support for a causal relationship.

Data quantity and data quality

The number of published epidemiologic studies on both diesel exhaust and ETS is large and quite comparable. The NTP identifies in Tables 3-1 and 3-2 six cohort studies and eight case control studies of cancer and diesel exhaust exposure. However, a recent meta-analysis by Bhatia, Lopipiero and Smith (1998) cites a somewhat larger epidemiologic research literature. They evaluated 29 studies of diesel exhaust and lung cancer. The authors included in their meta-analysis 21 of 23 studies that met their criteria. The NTP background document focuses attention on 30 or so ETS studies that have been published since the IARC review in 1986.

It is clear that both ETS and diesel exhaust exposure have received a good deal of epidemiologic research attention. If the sheer quantity of data could be used to resolve questions about the causal nature of an epidemiologic relationship, there should be no question at this point about either exposure. Of course, the quantity of data is not an adequate measure of what is known about either exposure. Data quality is independent of data quantity, and weaknesses in the underlying study designs restrict data quality in ways that cannot be overcome by simply repeating the same basic study over and over. This problem seriously limits interpretation of both the diesel exhaust and the ETS association with lung cancer risk. Both diesel exhaust and ETS epidemiologic studies use indirect proxy measures of exposure, collect inadequate information on possible confounding exposures, and introduce sources of bias that could account for any observed weak association. Publication bias, recall bias, and smoker misclassification bias are all likely to have influenced ETS epidemiologic research. No amount of repetition of the same basic study design will eliminate these underlying problems. Only better data from improved or entirely different designs will add to our understanding of the associations that have been reported.

Conclusion.

In choosing to classify diesel exhaust as a "reasonably anticipated" carcinogen the NTP indicates that it does not consider the diesel exhaust research to be strong enough to support a causal inference. I strongly agree with that conclusion. I also believe that the diesel exhaust research is comparable in both quantity and quality to the ETS research. There are in fact special problems of systematic bias in the ETS studies that make their interpretation even more ambiguous than the studies of diesel exhaust. I do not believe that the reported ETS / lung cancer association is causal, and I certainly do not believe that the data are strong enough to draw a causal inference. It is inconsistent of the NTP to apply different classifications to ETS and diesel exhaust when the underlying research is equally weak in both areas.

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