A REVIEW OF THE EXECUTIVE SUMMARY OF EPA'S DRAFT ETS RISK ASSESSMENT

CLAIM I: "Statistical significance. The two completed cohort studies and sixteen of the 21 case-control studies observed a higher occurrence of lung cancer among the female never-smokers classified as exposed to ETS. Evaluation of the total study evidence from several perspectives leads to the conclusion that the observed association between ETS exposure and increased lung cancer occurrence is not attributable to chance."

RESPONSE: Of the 23 published studies on ETS and lung cancer in nonsmokers, only five report statistically significant increased risks. This means that the data in 18 of the 23 studies do not permit rejection of the null hypothesis, i.e., there is no association between ETS exposure and lung cancer in nonsmokers. (Layard, McGill Symposium 1990)

Perhaps as a result of the failure of individual studies to report consistently significant results, certain researchers have recently begun using another method of statistical analysis which combines the reported results from numerous studies. With this method, called "meta-analysis," they claim to have calculated estimated excess risks

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for nonsmokers exposed to ETS that are 10 to 50 percent greater than those for nonexposed nonsmokers. In basic terms, they have reached these broad conclusions or "generalizations" by calculating an average of the relative risks for nonsmoker lung cancer cases reported by those studies.

However, this method of generalization has been criticized for its questionable application to the epidemiological studies on ETS, due to the wide variety in their study designs, population section, techniques of analysis and their results. This method also ignores basic methodologic weaknesses which, according to one recent governmental report, are characteristic of each published study on ETS and lung cancer. It further ignores the fact that the majority of studies considered in the various "meta-analyses" do not report statistically significant increases in lung cancer risks for nonsmokers. For example, only two of the thirteen studies considered by the 1986 NAS Report achieved

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statistical significance. (Although the authors of several studies report risks which are not statistically significant, they report "positive" trends in their data. However, trends which fail the test for statistical significance do not disprove the hypothesis that there is no relationship between ETS exposures and lung cancer)

In a recent analysis, Letzel and co-workers assessed the epidemiological studies on ETS for scientific rigor and then performed a meta-analysis on the data pooled from those studies. (Letzel, 1988) There were 1023 possible combinations in the ten case-control studies examined by the researchers; only twenty-four of those combinations gave rise to statistically significant results. Moreover, the statistical significance in those twenty-four combinations were dominated by the presence of three studies of questionable scientific merit. The authors therefore concluded that any computed excess risk would be negligible and could not be

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used to support the claim that ETS exposures increase the risk of lung cancer in nonsmokers.

CLAIM II "Cohort studies. Of the two major cohort studies, the Japanese study (Hirayama) demonstrates a strong association between passive smoking and lung cancer, including an upward trend in dose response. This study has undergone extensive critical review that led to some corrections and revisions, but failed to discredit the findings. Differences in life-style and culture may be a factor in the Japanese study reporting a stronger association between ETS and lung cancer than the American study (American Cancer Society)."

RESPONSE: The Executive Summary of the EPA Draft Risk Assessment correctly notes that the Hirayama study has been extensively criticized in the scientific literature The EPA Draft Executive Summary, however, is incorrect in its suggestion that the study has survived critical review. For example, in 1989, researchers reported that Hirayama had incorrectly adjusted the age of his study population (based on the husband's age) and that when correct age adjustments (based on the wife's age) are performed, the Hirayama study fails to achieve statistical significance. (Ahlborn & Uberla, 1988; Kilpatrick & Viren, 1988)

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CLAIM III: "Upward trend in dose-response. The upward trend in dose-response observed in the Hirayama study is well supported by the preponderance of evidence in the 13 case-control studies that classified data by exposure level."

RESPONSE: (Quoted from Layard, McGill University Symposium on ETS, p. 103): "Dose-Response Relationship. A dose-response relationship means that as the extent of exposure and hence the amount of dose increases, so too does the incidence of the outcome. In assessing the existence of a dose-response relationship, the non-exposed subjects are not considered. None of the 23 studies discussed above demonstrate a statistically significant dose-response relationship. The Japanese cohort study of Hirayama reported an inconsistent dose-response relationship when the subjects were stratified by the wife's age at the time of entry into the study (Hirayama 1984), as shown in Figure 6-1. Also, in the large American Cancer Society cohort (Garfinkel 1981), women whose husbands smoked 20 or more cigarettes per day had a lower relative risk (1.0) than those whose husbands smoked 1-19 cigarettes

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per day (1.27). Lack of a dose-response relationship is an internal inconsistency in a study which increases the likelihood that an observed association is due to the effects of bias or confounding, rather than to an effect of exposure."

CLAIM IV : "Detectable association at environmental exposure levels. The excess lung cancer rate among ETS-exposed persons is large enough to be statistically detected at environmental levels. This indicates a much higher response than most potential carcinogens wherein hazards are typically detectable only in high exposure circumstances, such as occupational settings or in highly dosed experimental animals."

RESPONSE : Animal inhalation experiments using sidestream smoke or constituents of sidestream smoke provide little support to the claim that ETS exposure is associated with lung cancer (Adlkofer, 1988) (Haley, 1986, 1987, 1988) (Aviado, 1988). German scientists exposed rats and hamsters to very high levels of sidestream smoke during a 90-day inhalation experiment. (Adlkofer, 1988) The researchers reported no significant physiological effects on the tissues of the animals.

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In his comprehensive review of the literature on suspected pulmonary carcinogens, Dr. Domingo Aviado observed that none of the constituents in sidestream smoke which have been identified as potentially carcinogenic has induced pulmonary cancer in animals under experimental inhalation conditions. (Aviado, 1988)

CLAIM V : "Broad-based evidence. The 21 case-control and three prospective studies provide data from eight different countries and from a wide variety of study designs and protocols conducted by many different research teams. No alternative explanatory variables for the observed association between ETS and lung cancer have been indicated that would be broadly applicable across studies."

RESPONSE : Genetic factors, different diets, and different exposures to occupational and domestic substances may account for reported lung cancer rates among nonsmokers in different parts of the world. This is particularly true in Hong Kong and China, where nonsmoker lung cancer rates among nonsmoking women are excessively high. Research by Koo and others (1988, 1989) on diet and other exposures

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reports that spousal smoking does not account for this high incidence.

Given the fact that most of the studies on ETS and lung cancer do not control for genetic factors, other exposures, diet, etc., the EPA's Executive Summary claim to "broad-based evidence" is dubious.

CLAIM VI: "Effects remain after adjustment for potential bias. Current and ex-smokers may be misreported as never-smokers, thus inflating the apparent cancer risk from ETS exposure. The evidence remains statistically conclusive, however, after adjustments for smoker misclassification. The summary estimate of relative risk from raw data of both the case-control and cohort studies is 1.41 (95% C.I. 1.26, 1.57) before adjustment for misclassification and 1.28 (95% C.I. 1.12, 1.45) afterward (P<0.01)."

RESPONSE: Other forms of misclassification are equally important and have not been addressed in the ETS-lung cancer studies. These kinds of misclassification include the misclassification of disease and misclassification of exposure. For disease, few researchers have histologically confirmed the presence of actual primary lung cancers. In addition, all studies assessed exposure

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through questionnaires of various forms. Questionnaires are a notoriously inaccurate way to assess exposure. No actual exposure samples were taken in any study.

CLAIM VII : "Biological plausibility. ETS is taken up by the lungs and distributed throughout the body. The similarity of carcinogens identified in sidestream smoke and mainstream smoke along with the established causal relationship between lung cancer and smoking make it reasonable to suspect that ETS is also a lung carcinogen."

RESPONSE : It is inaccurate to suggest that sidestream smoke components (the smoke measured at the burning end of the cigarette) are quantitatively similar to those found in highly diluted and aged ETS. Indeed, research suggests that typical nonsmoker exposure to ETS is less than one-one hundredth to one-one thousandth that of the nicotine equivalent of a single cigarette per hour. (See, e.g., Hinds and First, 1975; Murumatsu, 1984; Jenkins, 1988; Carson and Erickson, 1988; Oldaker, 1987)

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